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Webappendices for:

"Global patterns of opioid use and dependence: Population harms, interventions, and future action"

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Appendix A: Summary of overall approach to reviewing literature for this paper

This section summarises the broad approach used in searching for evidence during the writing of this paper.

- We systematically searched for high-quality reviews that involved quantitative synthesis where appropriate, in preference to other kinds of reviews. Details of the search strategies used for each component of the paper are summarised in this appendix.
- If no such review could be located, we selected narrative reviews if they clearly described the search strategy and inclusion/exclusion criteria for their review.
- If no such reviews could be located, we conducted searches for high quality single studies with the highest possible quality level for the issue being examined (e.g. well-conducted randomised controlled trials if searching for evidence on an intervention's efficacy).
- If no such studies could be located, we included lower-quality evidence but noted this clearly in tables and text.
- For some key areas, e.g. overdose, only older reviews could be located ([1,2]), so we conducted new full systematic reviews to update and expand upon previous reviews.

Panel A1: Types of opioids

Opioids are substances that stimulate opioid receptors in the body and brain. They can relieve pain, produce euphoria and in high doses, cause respiratory depression, loss of consciousness, overdose and sometimes death. A range of naturally occurring, semi-synthetic and synthetic opioids are produced and are used for medicinal and non-medicinal purposes. Opioids can either partially or fully stimulate opioid receptors, resulting in differing pharmacological responses.

- **Natural opioids (also known as opiates):** Derivatives of naturally occurring alkaloids found in the opium poppy, including morphine, codeine, and opium;
- **Semi-synthetic opioids**: Substances synthesised from naturally occurring opioids, including oxycodone, hydrocodone, hydromorphone, oxymorphone, and heroin (i.e., diacetylmorphine);
- **Synthetic opioids**: Class of drugs designed to mimic naturally occurring opioids, including methadone, fentanyl, pethidine (meperidine), levorphanol, tramadol, tapentadol and dextropropoxyphene.
- **Synthetic opioids considered novel psychoactive substances (NPS)**, which particularly include NPS fentanyl analogues such as acetylfentanyl, acryloyfentanyl, butyrylfentanyl, carfentanil, furanylfentanyl ocfentanyl, methoxyacetylfentanyl, and tetrahydrofuranylfentanyl.

Web appendix B: Evidence on medicinal uses of opioids

The WHO's Model list of essential medicines[3] was searched to obtain details of the opioid recommended for medicinal use. It lists codeine, fentanyl, morphine and methadone as opioid analgesics for pain and palliative care. Methadone and buprenorphine are listed for use in the treatment of opioid dependence.

We searched the Cochrane library for reviews of evidence for the use of opioids in treatment of pain, palliative care and opioid dependence. This resulted in 84 reviews that were considered for inclusion. These are listed below. A subset of these were used in the below panel to highlight examples of the nature of evidence for opioids in these indications; the full list of papers is below.

Panel B1: Medicinal uses of opioids

The WHO's Model List of Essential Medicines[3] lists codeine, fentanyl, morphine and methadone as essential medicines for pain and palliative care, and methadone and buprenorphine as essential medicines for use in the treatment of opioid dependence. The reference list below contains details of the reviews of evidence for opioids identified in Cochrane, some of which are mentioned below.

Acute pain: Opioids may be used in acute pain conditions including postoperative pain, pain management in labour[4], and conditions such as acute pancreatitis[5] and abdominal pain[6]. Low dose and usually less potent opioids are typically used in acute pain (e.g. codeine[7], 5 or 10 mg oxycodone[8]. There is increasing attention being given to the fact that long-term opioid prescribing can arise out of initial prescribing for an acute pain condition[9].

Cancer pain: Pain is a common occurrence in people living with cancer and often increases as cancers become more advanced. A recent Cochrane overview concluded that although the amount and quality of evidence on opioids for cancer pain was low, perhaps 19 out of 20 people with moderate to severe cancer pain would derive significant benefit within 14 days; between 10-20% of people would experience intolerable adverse events and change treatments[10]. A range of opioids are used in cancer pain; first-line being morphine[11], fentanyl[12], oxycodone[13] and methadone[14]. Limited evidence suggests hydromorphone[15] and tapentadol[16] may have similar outcomes compared to morphine or oxycodone. One review concluded buprenorphine should not be considered a first-line opioid for cancer pain[17]; another concluded tramadol may be less effective than morphine[18].

Chronic non-cancer pain (CNCP): There is limited, typically low-quality evidence from short-term randomised-controlled trials (RCTs) that opioids in adults living with CNCP may provide

some benefit[19,20], but little long-term evaluation[21]. Reviews of specific opioids in specific CNCP conditions such as neuropathic pain have concluded there is limited evidence for some (e.g. oxycodone[22]) and insufficient evidence for others (e.g. fentanyl[23], hydromorphone[24], buprenorphine[25]). No RCTs have been undertaken in young people living with CNCP[26]. There is a lack of evidence of efficacy of high dose (200mg oral morphine equivalent (OME) per day) for CNCP, even in the short term[27]. The 2016 US CDC guidelines[9] recommend that clinicians should avoid prescribing opioids, instead prescribing non-pharmacological interventions or non-opioid medications. They placed focus on whether opioids are indicated, careful opioid selection, low dose (<90mg OME/day) and limited prescribing duration.

Opioid withdrawal: using methadone[28] or buprenorphine[29] in a tapered fashion to manage withdrawal in opioid dependent adults increases likelihood of completing withdrawal (although most people will relapse to opioid use[28]); it is also associated with overdose and death after completion if people return to use. Completion of withdrawal is improved when psychosocial interventions are also delivered[30]. Limited evidence suggests opioids used to manage neonatal abstinence syndrome (NAS) reduce time to increased birthweight, but also increase length of hospital stay[31].

Opioid agonist treatment (OAT): Table 2 in the paper outlines evidence for OAT impacts, which occur across multiple domains. Higher doses of both methadone[32] and buprenorphine[33] have been found to improve retention in treatment and reduce extra-medical opioid use (among other outcomes); low-dose buprenorphine has poorer retention than high-dose methadone[33]. For those who do not respond to methadone or buprenorphine, diacetylmorphine (i.e., pharmaceutical heroin) increases retention and improves health and social outcomes[34] (see **Panel E** for discussion of injectable OAT).

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Web appendix C: Details of process for reporting and processing of data on opioid analgesic consumption reported to the International Narcotics Control Board

Please see below the description from INCB of the process for collecting and reporting on data on opioid analgesic consumption:

The 1961 Convention, which was expanded and strengthened by the 1972 Protocol, consolidated all previous conventions and streamlined the international drug control machinery. The 1961 Convention establishes strict controls on the cultivation of opium poppy, coca bush, cannabis plant and their products, which, in the Convention, are described as "narcotic drugs" (although cocaine is a stimulant drug rather than one that induces sleep). Control is exercised over 124 narcotic drugs, mainly natural products, such as opium and its derivatives, morphine, codeine and heroin, but also synthetic drugs, such as methadone and pethidine, as well as cannabis and coca leaf. Parties to the 1961 Convention undertake to limit the production, manufacture, export, import, distribution and stocks of, trade in and use and possession of the con-trolled drugs so that they are used exclusively for medical and scientific purposes. The production and distribution of controlled substances must be licensed and supervised, and Governments must provide estimates and statistical returns to INCB on the forms supplied for that purpose, on the quantities of drugs required, manufactured and utilized and the quantities seized by police and customs officers. The control system established under the 1961 Convention functions well, and the system of estimates first introduced by the 1931 Convention is considered to be the key to that success. The system of estimates covers all States, regardless of whether or not they are parties to the 1961 Convention. Each year, INCB publishes in a technical publication information about the licit movement of the internationally controlled narcotic drugs.

All national competent authorities have to submit to INCB the following forms with the information Governments are required to furnish to the Board pursuant to the provisions of the Single Convention:

Form A (Quarterly Statistics of Imports and Exports of Narcotic Drugs; to be submitted four times a year);

Form B (Annual Estimates of Requirements of Narcotic Drugs, Manufacture of Synthetic Drugs, Opium Production and Cultivation of the Opium Poppy for Purposes other then Opium Production); and

Form C (Annual Statistics of Production, Manufacture, Consumption, Stocks and Seizures of Narcotic Drugs).

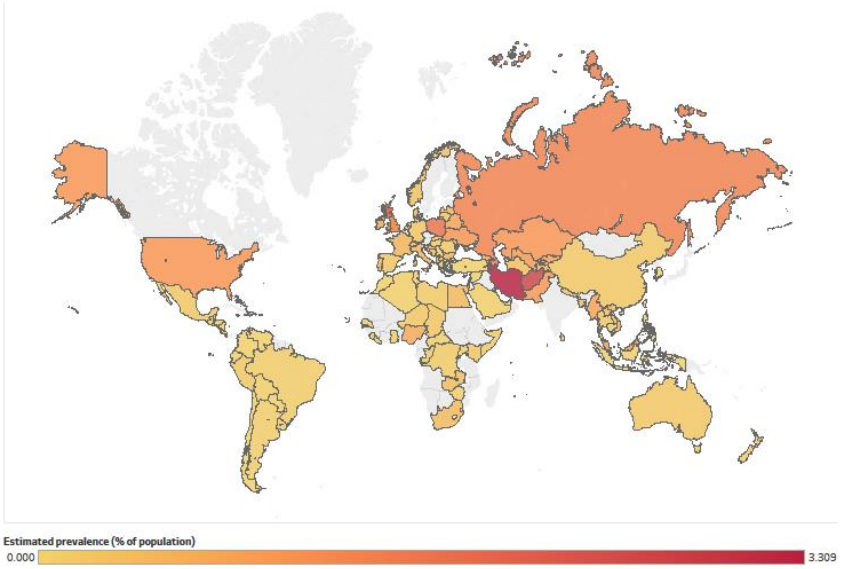
If any Government has to modify its estimates, which were furnished to INCB in Form B, the national competent authority shall send to INCB the form entitled Supplement to Form B (Supplement to the Annual Estimates of Requirements of Narcotic Drugs).

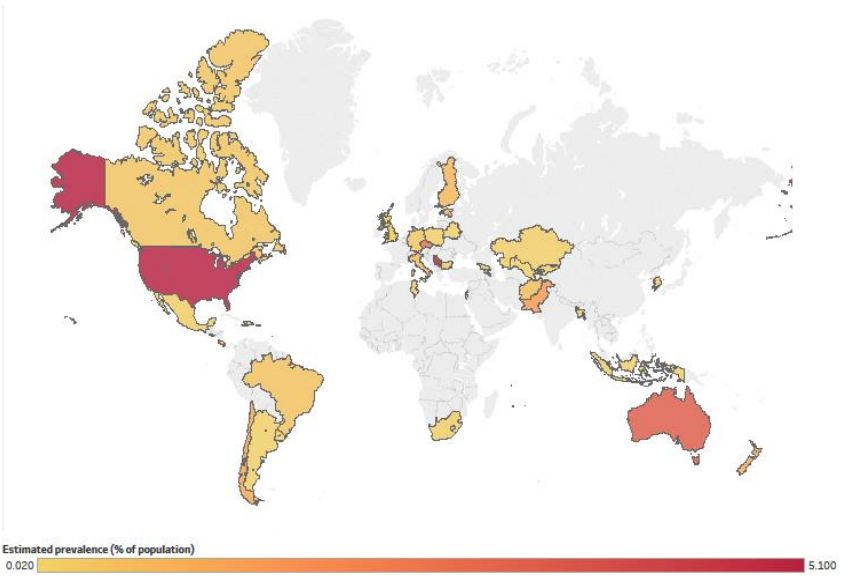
Web Appendix D: Data on the prevalence of opioid use collected by the United Nations Office on Drugs and Crime

Data on the annual prevalence of opioids use as a percentage of the population age 15-64 were obtained from the UNODC World Drug Report 2018, available from https://www.unodc.org/wdr2017/en/maps-and-graphs.html. Data from individual countries are mainly sourced from UNODC's Annual Report Questionnaire (ARQ), which collects and reports data on extent, patterns and trends in drug use and its health consequences across the world. The World Drug Report also incorporates data from the literature and grey literature, such as from government sources, academic research, and major international surveys that monitor drug use.

Estimates of the prevalence of opioid use are computed using various adjustments. The figure below presents UNODC's estimates of the prevalence of opiate and extra-medical pharmaceutical opioids in the past year for 2016.

Figure D1: Past-year prevalence of opiate use (top) and extra-medical use of pharmaceutical opioids (bottom)





Source: United Nations Office on Drugs and Crime's 2018 World Drug Report[35] data tables.

Appendix E: Summary of review of extent of pharmaceutical opioid use and dependence

Ellerstrand et al (2018)[36] conducted a systematic review of the prevalence of the prevalence of illicit and pharmaceutical opioid (PO) nonmedical use and dependence by country were extracted. The search for this study was undertaken as a part of the GBD 2016 study on the global prevalence of substance dependence. Multiple research strategies were utilised, including systematic searches of peer-reviewed literature and collaboration with experts in the field. The choice of databases was selected in concert with expert opinion as well as discussion with university research librarians. A systematic search of peer-reviewed literature was performed using Medline, Embase and PsycINFO databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) style was employed [37].

Search terms were grouped into: 1. substances; 2. use or dependence; 3. database specific terms representing substance dependence (eg. MeSH or Emtree terms); and 4. epidemiology measures (eg. prevalence). Search strategy was grouped as ((1 AND 2) OR 3) AND 4. Epidemiological search strings were standardised for the Psychiatric Epidemiology and Burden of Disease Group (PEABOD team) of which the researchers were a part. This team researches mental and substance use disorders in the GBD study. Search limitations comprise publication year from 2009 onwards (as the last systematic review on opioid dependence was conducted in 2009), peer reviewed journal articles and human studies. There were no limits set on language; the research team included translators. All stages of screening were performed by two reviewers. Data extraction was conducted simultaneously with full-screen review i.e. if an article was selected for inclusion, it was immediately extracted.

Web appendix F: Details of Global Burden of Disease 2017 study data for opioid dependence and opioid overdose

Burden was quantified by geography, for 20 age groups covering 0-99 years, both sexes, and timepoints spanning the period 1990 to 2017. Comprehensive methods for estimating YLDs, YLLs, and DALYs have been presented in a series of publications[38-41]

YLLs

Input data on causes of death data came from vital registration, verbal autopsy and surveillance databases dating back to 1980.[38,41] Normative life tables were generated using data on the lowest death rates for each age group within geographies with total populations of more than 5 million. YLLs were then estimated by multiplying cause-specific deaths at a given age by the standard life expectancy at that age obtained from this normative life table. Full details of all the modelling process have been published previously.[38,41]

The Cause of Death Ensemble modelling (CODEm) strategy was used to model cause of death data by location, age, sex, and year for opioids.[38,41] CODEm model outputs for all GBD causes were then rescaled to fit the all-cause mortality envelope to derive final cause-specific deaths; deaths coded as alcohol and drug poisonings were attributed to the relevant alcohol and drug use disorders.

YLDs

Epidemiological disease models

Systematic reviews of the literature were conducted to compile data on the prevalence, incidence, remission, and excess mortality associated with opioid dependence. Electronic databases (PubMed, EMBASE, PsycINFO) and grey literature sources were searched in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.[42] For each epidemiological parameter, eligible estimates were derived from studies published since 1980.

The epidemiological data obtained from systematic literature reviews were modelled in DisMod-MR 2.1. This is a Bayesian meta-regression tool which pools data-points from different sources and adjusts for known sources of variability (e.g. differences in case definitions and sampling method) to produce internally consistent estimates of incidence, prevalence, remission, and excess mortality.[43] It is also used to estimate the epidemiology of disorders within areas with limited data.

DisMod-MR 2.1 analyses ran in a sequence of estimations at each level of the GBD geographic hierarchy (global, super-region, region, country, and if applicable, subnational locations) with consistency imposed between estimates at each level. More information on DisMod-MR 2.1 has been presented in other publications.[38-41]

Although our inclusion criteria ensured minimum study quality, there was considerable variability between studies that reflected different methodologies and analyses (e.g. see[44-48]). Uncertainty in both the epidemiological data and in modelling was propagated to the final prevalence output used to calculate YLDs. This was in addition to the uncertainty from fixed effects and random effects for country and regions.[43]

Disability weights

Each country, age, sex, and year-specific prevalence derived by DisMod MR 2.1 was multiplied by a disorder-specific disability weight to estimate YLDs. Disability weights ranged from 0 ('perfect health') to 1 ('death') to quantify the severity of the health loss associated with a given disease or injury. They were obtained from population surveys in a number of different countries and from an open-access survey available in multiple languages in which lay participants were presented with pairs of short descriptions of health states and asked to rate which they considered the more 'unhealthy'.[49-51] Disability weights were generated for all sequelae of diseases and injuries. Further details regarding disability weight methodology has been published previously[50-52].

Disability-adjusted life-years (DALYs)

The burden calculation involved (1) aggregating substance use disorder-specific epidemiological data and disability weights to calculate prevalent YLDs[40]; (2) multiplying substance use disorder-specific estimates of mortality by standard life expectancy at the age of death to calculate YLLs[38,41]; and (3) summing YLDs and YLLs to generate substance use disorder-specific DALYs[39].

DALYs were derived by summing YLD and YLLs for each disorder, location, age group, sex, and year. Age-standardised rates of prevalence, deaths, YLLs, YLDs, and DALYs were estimated using the GBD world population age standard. Uncertainty was derived for all estimates by simulating 1000 draws from each estimate's posterior distribution. This captures uncertainty arising from primary inputs, sample sizes in the data collected, adjustments made to the data during modelling, and model estimation. For YLLs, they capture uncertainty due to study sample sizes, adjustments made to the all-cause mortality data, and model estimation.

Appendix Table F1: Regional and global estimates of the prevalence and number of cases of opioid dependence estimated in the Global Burden of Disease study 2017

	Opioid dependence		Opioid overdose deaths	
Location	Cases of opioid dependence (1000s) (95%UI)	Age-standardised rate per 100,000 (95%UI)	Number of opioid deaths (1000s) (95%UI)	Age-standardised overdose rate per 100,000 (95%UI)
Andean Latin America	205.79 (169.91 - 248.55)	331.19 (274.4 - 397.30)	0.48 (0.42 - 0.54)	0.84 (0.74 -0.94)
Australasia	124.07 (105.71 - 144.66)	430.27 (363.31 - 507.77)	0.69 (0.60 - 0.79)	2.19 (1.90 - 2.52)
Caribbean	155.12 (127.32 - 185.88)	319.47 (261.98 - 383.75)	0.31 (0.28 - 0.35)	0.63 (0.56 - 0.70)
Central Asia	202.10 (169.27 - 239.75)	208.65 (176.12-246.45)	1.17 (1.08 - 1.29)	1.30 (1.21 - 1.43)
Central Europe	225.37 (191.84 - 263.90)	179.21 (149.73 - 212.86)	0.73 (0.69 - 0.77)	0.5 (0.47 - 0.53)
Central Latin America	875.53 (724.77 - 1057.10)	330.94 (274.96 - 399.12)	1.71 (1.64 - 1.79)	0.68 (0.65 - 0.71)
Central sub-Saharan Africa	353.71 (286.13 - 437.21)	335.12 (275.11 - 408.19)	0.46 (0.33 - 0.60)	0.53 (0.38 - 0.70)
East Asia	10,501.21(8,745.54 – 12,643.64)	622.21 (509.85 - 759.44)	15.75 (14.81 -16.86)	0.85 (0.80 - 0.91)
Eastern Europe	712.91 (606.90 - 834.42)	307.76 (258.42 - 366.14)	8.26 (7.82 - 8.81)	3.31 (3.13 - 3.54)
Eastern sub-Saharan Africa	988.30 (794.10 – 1,241.43)	294.72 (242.63 - 361.19)	0.68 (0.44 - 0.91)	0.28 (0.17 - 0.37)
High-Income Asia Pacific	497.33 (418.84 - 588.46)	260.54 (212.96 - 317.09)	0.55 (0.53 - 0.58)	0.19 (0.186 - 0.20)
High-Income North America	4,751.86 (4,058.04 – 5,574.96)	1,347.66 (1,136.95 – 1,609.35)	48.63 (45.10 - 52.08)	12.31 (11.46 - 13.14)
North Africa and Middle East	9,286.71 (7,733.90 – 11,004.65)	1,459.36 (1,226.44 – 1,718.77)	8.31 (7.77 - 9.04)	1.46 (1.37 - 1.58)
Oceania	29.78 (23.76 - 37.68)	244.06 (198.40 - 305.06)	0.02 (0.009 - 0.03)	0.18 (0.10 - 0.25)
South Asia	6,331.35 (5,141.18 – 7,769.83)	346.80 (284.75 - 421.59)	8.14 (6.10 - 9.37)	0.53 (0.39 - 0.61)
Southeast Asia	1,330.32 (1,099.55 -1,622.60)	189.16 (156.40 - 230.81)	3.02 (2.77 - 3.28)	0.46 (0.42 - 0.50)
Southern Latin America	183.96 (151.39 - 225.12)	264.69 (215.46 - 326.73)	0.52 (0.47 - 0.58)	0.67 (0.61 - 0.75)
Southern sub-Saharan Africa	426.59 (349.60 - 523.44)	516.09 (428.18 - 625.68)	0.65 (0.58 - 0.78)	0.86 (0.77 - 1.03)
Tropical Latin America	796.39 (964.86 - 656.66)	333.88 (275.23 - 404.91)	1.31 (1.26 - 1.38)	0.56 (0.53 - 0.58)
Western Europe	1,188.14 (1037.55 – 1,343.14)	262.50 (226.55 - 300.27)	5.06 (4.86 - 5.41)	1.02 (0.98 - 1.10)
Western sub-Saharan Africa	1,318.05 (1077.19 – 1,606.51)	356.12 (297.96 - 424.97)	3.05 (2.40 - 3.82)	0.98 (0.80 - 1.25)
Global	**40,484.59 (34,271.36 – 47,941.59)**	**510.28 (430.32 - 605.55)**	**109.52 (105.75 – 113.56)**	**1.37 (1.32 - 1.42)**

Web appendix G: Literature on mechanisms and consequences of opioid overdose

Search strategy

This section was written following a series of literature searches. These were performed on PubMed and included searches for 'heroin OR morphine OR opioid' and each of the following terms – pulmonary function, pulmonary oedema, respiratory depression, brain imaging, brain damage, apoptosis, cognitive function, poly drug use, poly pharmacology, pregabalin, gabapentin – as well as searches for 'fentanyl' and respiratory depression, muscle rigidity. Papers were extracted by the authors for their relevance to the topics being reviewed on the basis of their titles and abstracts. In addition, secondary references cited in extracted papers were consulted. Where available recent meta analyses are referenced.

Mechanisms of opioid overdose

At higher doses, opioids suppress respiratory rhythm generation and reduce normal physiological responsiveness of central and peripheral chemoreceptors. As a result, CO_2 levels rise and hypoxia develops[1]. Consequently, breathing rates decrease and eventually stop.

Though respiratory depression contributes most to fatal overdose, aspiration of oral or gastric contents may also occur. Time to opioid-related death is variable. Death can occur quickly (e.g. 10-30 minutes when injected), or longer when administered using other routes[2-4]. When more prolonged, other pathophysiological responses like respiratory acidosis, pulmonary oedema and aspiration pneumonia increase morbidity or can themselves result in death.

Fentanyl and its structural analogues are potent, highly lipid soluble opioids that rapidly enter the brain following intravenous injection, resulting in accelerated respiratory depression[5]. Though not fully understood[6], they also induce "respiratory paralysis" by promoting higher levels of chest wall rigidity by causing the respiratory intercostal and diaphragmatic muscles to constrict and prevent chest inflation[6], relative to other opioids.

For people who use opioids long-term, tolerance to opioids develops, requiring larger doses to either avoid withdrawal symptoms and/or achieve euphoria. Because tolerance to respiratory depression is believed to be less than it is for euphoria (or analgesia in animal models)[7], users will often increase the dose of opioids enhancing the effects of respiratory depression[7-9].

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Web appendix H: Details of literature search on other harms elevated among people who use opioids extra-medically

Review of reviews

Injecting risk behaviour

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86559
2	(inject* or injecting risk or (risk behaviour adj3 inject*)).ti,ab.	613357
3	1 and 2	12944
4	limit 3 to (human and yr="2000 -Current" and "review")	409

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151122
2	(inject* or injecting risk or (risk behaviour adj3 inject*)).ti,ab.	989749
3	1 and 2	18031
4	limit 3 to (human and yr="2000 -Current" and "review")	700

Dependence

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86559
2	((dependen$ or use-disorder) and risk).ti,ab.	65579
3	1 and 2	1643
4	limit 3 to (humans and yr="2000 -Current" and "review")	301

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151197
2	((dependen$ or use-disorder) and risk).ti,ab.	109741
3	1 and 2	3175
4	limit 3 to (human and yr="2000 -Current" and "review")	389

HIV incidence

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86559
2	(HIV adj3 incidence).ti,ab or (exp HIV/ and exp Incidence/)	5021
3	1 and 2	119
4	limit 3 to (human and yr="2000 -Current" and "review")	16

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151197
2	(HIV adj3 incidence).ti,ab. or (exp Human Immunodeficiency Virus/ and exp Incidence/)	8223
3	1 and 2	174
4	limit 3 to (human and yr="2000 -Current" and "review")	20

HIV injecting risk

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86559
2	(HIV adj3 inject*).ti,ab. or (exp HIV/ and (exp Intravenous Drug Abuse/ or inject*.ti,ab. or injecting risk.ti,ab.))	4365
3	1 and 2	432
4	limit 3 to (human and yr="2000 -Current" and "review")	31

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151197
2	(HIV adj3 inject*).ti,ab. or (exp Human Immunodeficiency Virus/ and (exp Intravenous Drug Abuse/ or inject*.ti,ab. or injecting risk.ti,ab.))	8231
3	1 and 2	875
4	limit 3 to (human and yr="2000 -Current" and "review")	55

HCV incidence

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	((exp Hepatitis C/ or "HCV".ti,ab.) and exp Incidence/) or (HCV adj3 incidence).ti,ab	2672
3	1 and 2	87
4	limit 3 to (human and yr="2000 -Current" and "review")	11

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151197
2	((exp Hepatitis C/ or "HCV".ti,ab.) and exp Incidence/) or (HCV adj3 incidence).ti,ab	5649
3	1 and 2	165
4	limit 3 to (human and yr="2000 -Current" and "review")	21

HCV injecting risk

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	((exp Hepatitis C/ or "HCV".ti,ab.) and (exp Intravenous Drug Abuse/ or inject*.ti,ab. or injecting risk.ti,ab.)) or (HCV adj3 inject*).ti,ab	4672
3	1 and 2	532
4	limit 3 to (human and yr="2000 -Current" and "review")	45

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151197
2	((exp Hepatitis C/ or "HCV".ti,ab.) and (exp Intravenous Drug Abuse/ or inject*.ti,ab. or injecting risk.ti,ab.)) or (HCV adj3 inject*).ti,ab	8407
3	1 and 2	1083
4	limit 3 to (human and yr="2000 -Current" and "review")	93

Skin and soft tissue infections

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	exp Injection site abscess/ or exp Skin Abscess/ or (skin and inject*).ti,ab.	19530
3	1 and 2	256
4	limit 3 to (human and yr="2000 -Current" and "review")	10

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Injection site abscess/ or exp Skin Abscess/ or (skin and inject*).ti,ab.	40822
3	1 and 2	504
4	limit 3 to (human and yr="2000 -Current" and "review")	25

Quality of life

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	exp Quality of Life/ or "QoL".ti,ab.	162841
3	1 and 2	796
4	limit 3 to (human and yr="2000 -Current" and "review")	153

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp "quality of life"/ or "QoL".ti,ab.	421252
3	1 and 2	4777
4	limit 3 to (human and yr="2000 -Current" and "review")	1163

Contact with criminal justice system

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581

#	Searches	Results
2	exp Offender/ or crim*.ti,ab. or (crim* adj3 behavi*).ti,ab. or (crim* adj3 act*).ti,ab.	30617
3	1 and 2	1041
4	limit 3 to (human and yr="2000 -Current" and "review")	106

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Offender/ or crim*.ti,ab. or (crim* adj3 behavi*).ti,ab. or (crim* adj3 act*).ti,ab.	50820
3	1 and 2	1666
4	limit 3 to (human and yr="2000 -Current" and "review")	178

Accidental injuries

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	accident$.ti,ab.	90615
3	1 and 2	500
4	limit 3 to (humans and yr="2000 -Current" and "review")	52

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	accident$.ti,ab.	149021
3	1 and 2	1168
4	limit 3 to (human and yr="2000 -Current" and "review")	104

Suicide

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86598
2	exp Suicide/ or exp Suicide Attempt/ or suicid*.ti,ab.	75479
3	1 and 2	677
4	limit 3 to (human and yr="2000 -Current" and "review")	51

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Suicide/ or exp Suicide Attempt/ or suicid*.ti,ab.	107675
3	1 and 2	1566
4	limit 3 to (human and yr="2000 -Current" and "review")	193

Overdose

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86581
2	((acute and toxic$) or overdos$).ti,ab.	69022
3	1 and 2	2614
4	limit 3 to (humans and yr="2000 -Current" and "review")	340

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	((acute and toxic$) or overdos$).ti,ab.	122589
3	1 and 2	5135
4	limit 3 to (human and yr="2000 -Current" and "review")	528

Neonatal outcomes

Preterm births

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86598
2	exp Premature labor/ or exp Prematurity/	22910
3	1 and 2	33
4	limit 3 to (human and yr="2000 -Current" and "review")	3

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Premature labor/ or exp Prematurity/	136777
3	1 and 2	564
4	limit 3 to (human and yr="2000 -Current" and "review")	130

Low birth weight

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86598
2	exp Birth Weight/	38213
3	1 and 2	160
4	limit 3 to (human and yr="2000 -Current" and "review")	5

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Birth Weight/	109790
3	1 and 2	505
4	limit 3 to (human and yr="2000 -Current" and "review")	56

Head circumference

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	86598
2	((infant or newborn) adj3 head circumference).ti,ab or (exp Infant/ and head circumference.ti,ab.)	3801
3	1 and 2	60
4	limit 3 to (human and yr="2000 -Current" and "review")	3

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Head Circumference/	10433
3	1 and 2	89
4	limit 3 to (human and yr="2000 -Current" and "review")	5

Neonatal abstinence syndrome

Medline search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp heroin/ or exp opioid-related disorders/	89598

2	neonatal abstinence syndrome.ti,ab or (exp Infant/ and (withdraw* or abstinence).ti,ab.)	4571
3	1 and 2	621
4	limit 3 to (human and yr="2000 -Current" and "review")	82

Embase search results

#	Searches	Results
1	(opioid or opiate or heroin).ti,ab. or exp opiate/ or exp heroin dependence/	151314
2	exp Neonatal Abstinence Syndrome/	336
3	1 and 2	184
4	limit 3 to (human and yr="2000 -Current" and "review")	33

Description of evidence base on other harms elevated among people who use opioids extra-medically

Injecting risk behaviour

Dependence

HIV incidence

HIV injecting risk

HCV incidence

HCV injecting risk

Skin and soft tissue infections

Quality of life

Criminal activity

Table H1: Self-reported arrests by gender rate ratios reported in Weissman, 1976

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Male	4.900	3.900	6.200	85.53
Female	11.400	4.900	26.500	14.47
Pooled rate ratio	5.841	1.358	10.323	100.00

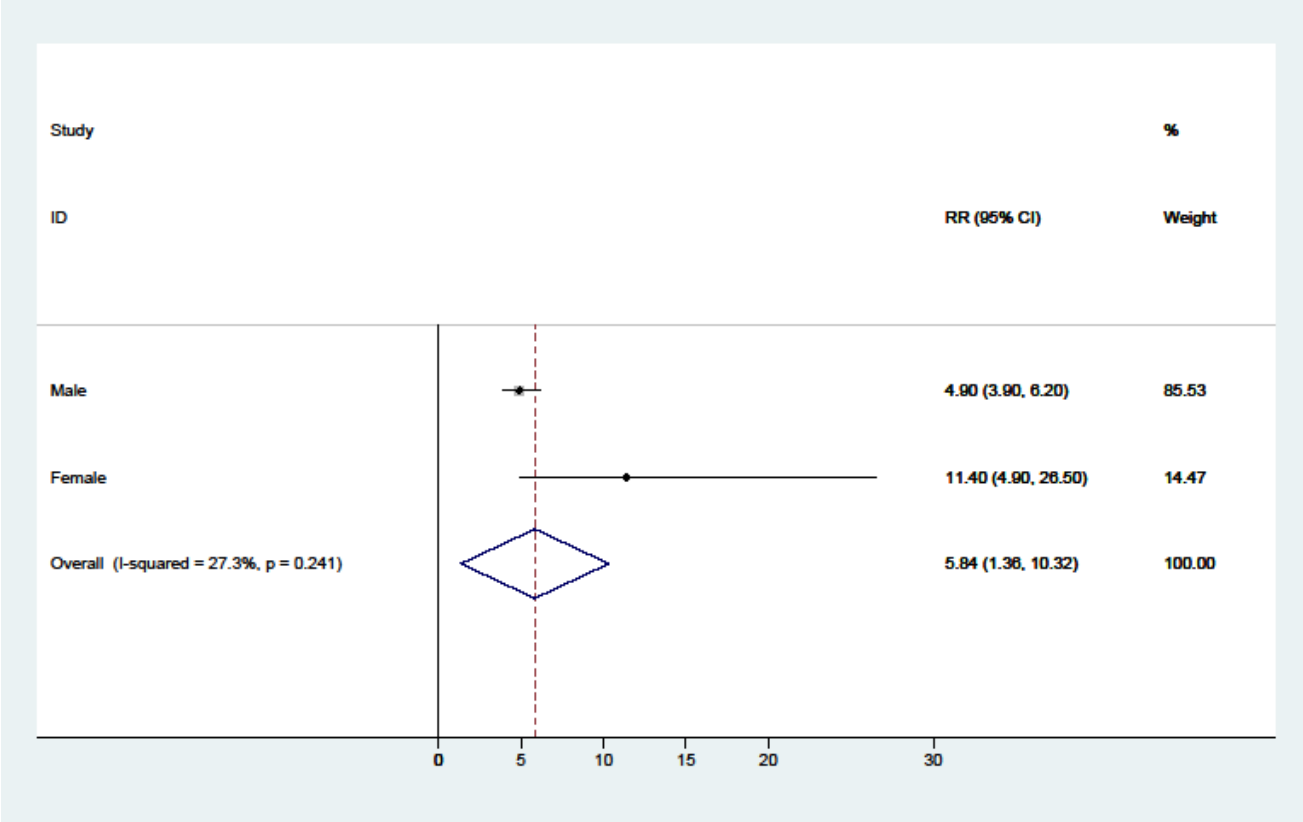


Figure I1: Pooled gender arrests rate ratios as reported in Weissman, 1976.

Contact with criminal justice system

Table H2: Total convictions rate ratios of studies identified via Hayhurst, 2017

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Alexander, 1974	0.710	0.400	1.300	20.58
Jarvis, 1989	2.200	1.500	3.100	19.83
Mott, 1974	1.400	1.100	1.700	20.79
Parker, 1987	4.600	3.800	5.600	19.55
Wiepert, 1979	6.200	5.300	7.300	19.25
Pooled rate ratio	2.966	1.426	4.506	100.00

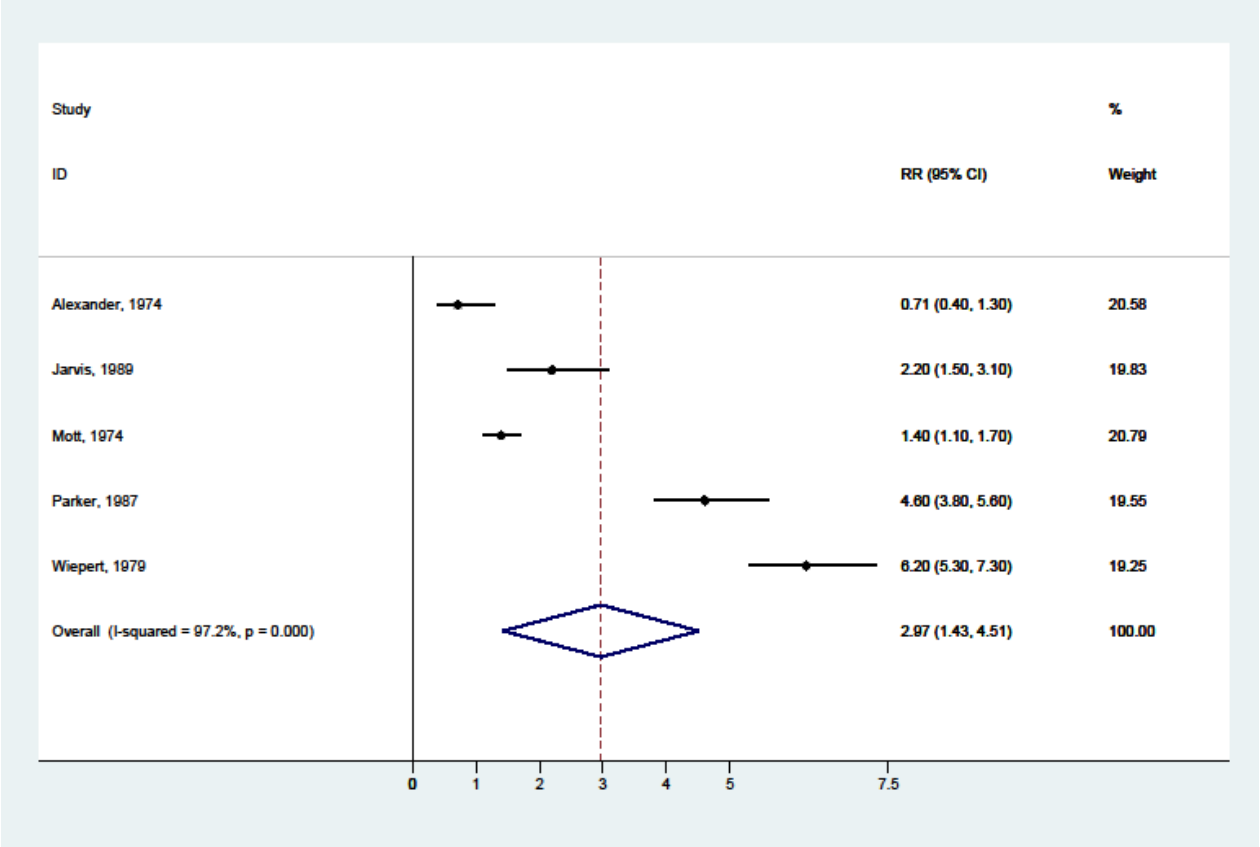


Figure I2: Pooled rate ratios of total convictions of studies identified through Hayhurst, 2017.

Accidental injuries

Suicide

Overdose

Neonatal outcomes

Preterm births

Low birth weight

Head circumference

Neonatal abstinence syndrome

Web appendix I: Details of literature search on mortality among people who use opioids, including fatal overdose

Description of methods

Studies identified in a previously published review will be used to identify studies published from 1980 to 2008.

The Medline, Embase and PsycINFO peer-reviewed literature databases will be searched using the OVID™ interface/platform for relevant articles published from the time-periods 2009 till current. Articles of interest comprise those likely to contain data describing all-cause and cause-specific crude mortality rates (CMR) and/or standardised mortality ratios (SMR) among people who use opioid, cocaine, or amphetamine-type stimulants. Sets of search strings incorporating both keywords and Medical Subject Headings (MeSH terms) reflecting drug type and mortality epidemiology from the previous reviews will be revised and expanded for this updated search. Searches will be limited to human literature. No other restrictions will be applied to the search; citations for papers in languages other than English will be included and read via Google Translate. Citations from these searches will be imported into an Endnote™ library, and duplicate citations removed.

To check for missing peer-review literature, reference lists for relevant systematic reviews identified in the peer-review literature search will be hand searched for additional papers not already identified. A final list of included studies will be distributed to experts to check if any relevant studies are missed.

Each set of search results (title and abstract) will first be screened by one team member in Covidence. All papers marked as excluded will be reviewed by a second person to ensure accuracy in first-pass screening. Each study for full-text screening will be reviewed in full by two people. Conflicts will be resolved through discussion and referral to a third party if needed.

Data will be independently extracted into an Excel worksheet template by one member of the research team and checked by a second member of the team. Bibliographic information will be extracted in addition to study specific information. Data entry will be standardized by use of a

manual, which contains data entry rules. Where data are incomplete, authors will be contacted via email to obtain additional information.

Variables extracted will include study information and sample information (treatment status, HIV status, sex, percentage of sample injecting, treatment engagement). Crude mortality rates (CMRs) and standardized mortality ratios (SMRs) will be extracted as mortality measures. Cause of death information will be extracted for AIDS, overdose, suicide, traumatic (accident, homicide, injury, violence and poisoning), disease-related deaths, and other key categories. Disease-related deaths will be recoded according to the following categories; cardiovascular (endocarditis, myocardial infarction, circulatory system disease and cardiovascular disease),cerebrovascular, respiratory (pneumonia and chronic respiratory disease), liver (cirrhosis, viral hepatitis and liver disease), cancer (neoplasm, tumour and carcinoma), digestive (digestive system disease, nephritis and haemorrhage from duodenal ulcer), nervous system disease and other diseases (tuberculosis, bacterial infection, unspecified 'other disease' or 'natural causes' and when disease categories are not separated).

The quality index used in the previous reviews will be adopted for consistency. The quality index assesses each study on nine individual criteria: case ascertainment, measurement, diagnosis, estimate, numerator and denominator, data catchment, completeness, representativeness and age/sex variables. Each criterion will include a rating scale and the individual scores tallied to provide an overall quality score. Study information necessary for quality assessment will be extracted to the Excel template. The greater the quality score, the higher the methodological quality of the study. Mortality estimates from higher rating studies may be given additional weighting in the calculation of final estimates. Quality estimates may also be used to undertake sensitivity analyses.

Crude mortality rates will be calculated as per 100 person-years. Where person-years are not reported nor made available by the authors, an approximate person-year of follow-up will be calculated, with the assumption that deaths occurred halfway through the follow-up period, so that each case contributes half the person-year follow-up of survivors.

Estimates will be analysed in subgroups according to population type (for example, estimates from cohorts recruited on the basis of having a chronic physical health condition associated with a high mortality rate may be considered separately). Random-effects meta-analyses to determine pooled all-cause and cause-specific CMR and SMR estimates will be performed using STATA. This approach

uses inverse variance weighting to calculate: fixed- and random effects pooled summary estimates; confidence limits; a test for differences between study effects; and an estimate of between-study variance. The random effects model allows for heterogeneity between as well as within studies; expecting high levels of heterogeneity between cohorts, the random-effects model will be used in all meta-analyses, with confirmation through the heterogeneity c2 and I-squared statistic. To investigate the source of this heterogeneity in an attempt to reduce it, cohorts may be divided into subsamples (e.g., by sex, age group, treatment status and HIV status) and/or these factors studied as possible risk factors for mortality via meta-regression in Stata.

Search strings for electronic literature searches

Database	Search group	Search terms
Medline*	Opioids	Heroin or opiate or opium or methadone or opioid morphine or buprenorphine or "OST" or "opiate substitution" or "MMT" or "methadone maintenance" or "buprenorphine maintenance" or "opioid replacement" or "opioid agonist" or "opiate agonist" or "opioid maintenance" or "opiate maintenance" or "opiate substitution" or "opiate replacement" **exp opium/ or exp narcotics/ or exp heroin dependence/ or exp Heroin/ or exp opioid-related disorders/ or exp opiate alkaloids/ or exp methadone/ or exp analgesics, opioids/ or exp opiate substitution treatment/ or exp buprenorphine/ or exp buprenorphine, naloxone drug combination/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp DEATH, SUDDEN/ or exp Fatal Outcome/ or exp Mortality/**
EMBASE#	Opioids	Heroin or opiate or opium or methadone or opioid or methadone or opioid or morphine or buprenorphine or OST or opioid substitution or MMT or methadone maintenance or buprenorphine maintenance or opioid replacement or opioid agonist or opiate agonist or opioid maintenance or opiate maintenance or opiate substitution or opiate replacement **exp Diamorphine/ or exp Opiate/ or exp methadone treatment/ or exp methadone/ or exp heroin dependence/ or exp opiate addiction/ or exp buprenorphine/ or exp buprenorphine plus naloxone/ or exp opiate substitution treatment/**
	Mortality	Mortal* or fatal* or death* **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp ACCIDENTAL DEATH/ or exp SUDDEN DEATH/ or exp Fatality/ or exp Mortality/**
PsychINFO^	Opioids	Heroin or opiate or opium or methadone or opioid or methadone or opioid or morphine or buprenorphine or "OST" or "opioid substitution" or "MMT" or "methadone maintenance" or "buprenorphine maintenance" or "opioid replacement" or "opioid agonist" or "opiate agonist" or "opioid maintenance" or "opiate maintenance" or "opiate substitution" or "opiate replacement" **exp Heroin addiction/ or exp Opiates/ or exp methadone/ or exp Heroin/ or exp methadone maintenance/ or exp buprenorphine/**
	Mortality	Mortal* or fatal* or death* **exp "DEATH AND DYING"/ or exp Mortality/ or exp Mortality Rate**

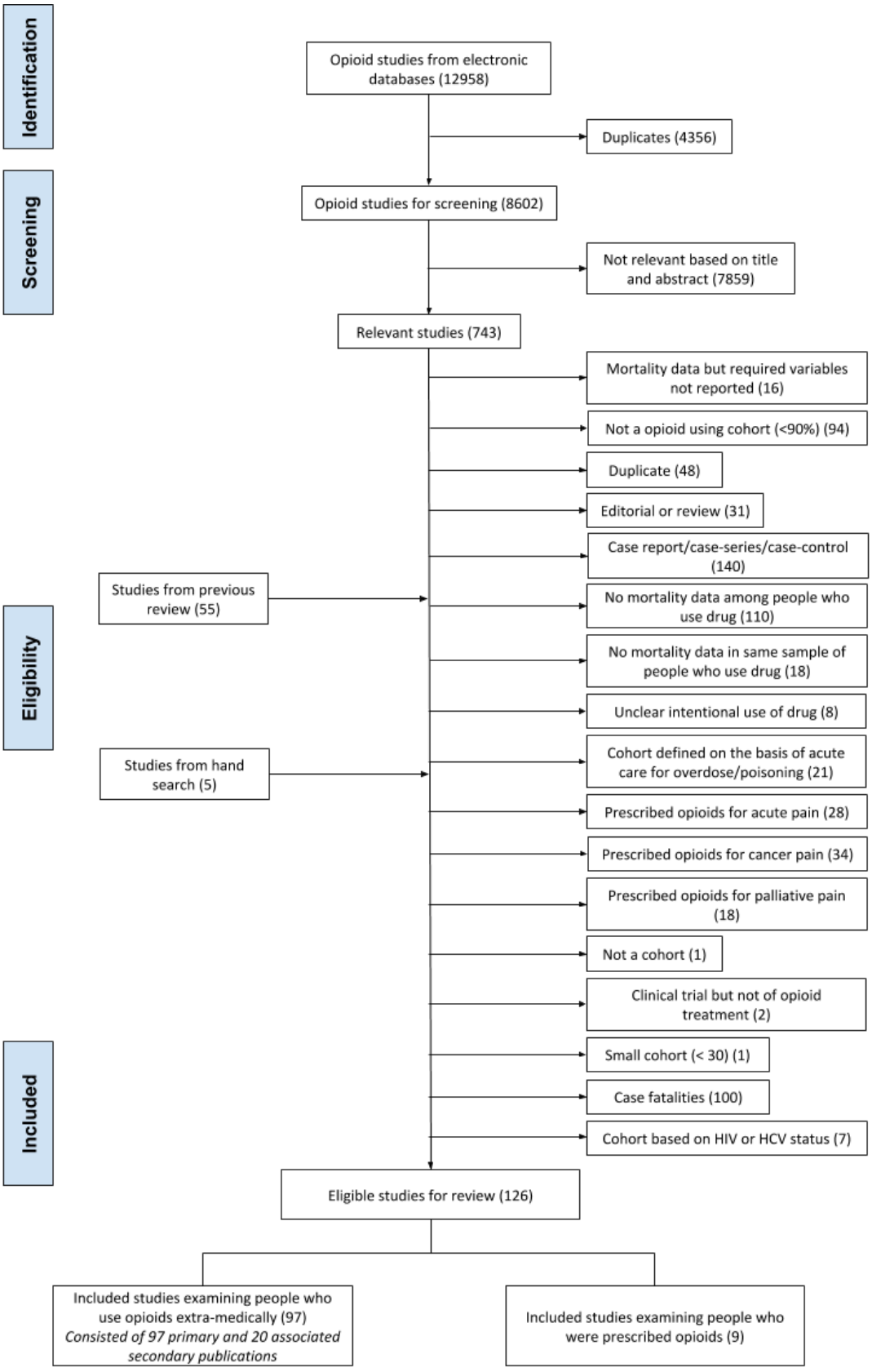
* 'key-words' in lowercase, 'MeSH' terms in **bold** # 'key-words' in lowercase, 'EMTREE' terms in **bold**

^ 'key words' in lowercase, explode terms in **bold**

Number of articles identified from opioid mortality search

	Search terms		Database		
			EMBASE	Medline	PsycINFO
1.	Opioids	+mortality	8357	3371	1230

PRISMA Flowchart of search strategy



List of included studies

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Web appendix J: Details of literature search on reviews of interventions to reduce adverse health outcomes

Description of Method

We used a multi-stage hierarchical searching process to identify sources reporting on the impact of various interventions on health outcomes associated with amphetamine and cocaine use amongst samples who report use of these substances.

The intent was to search for and identify the highest quality study type (see Table 1) for each intervention and the associated health outcome.

Table 1. Classification system used in assessment of study methodologies

Level	Study type
1	Systematic review of all relevant randomised controlled trials
2	Properly designed randomised controlled trial
3.1	Well-designed pseudorandomised controlled trials [alternate allocation or some other method]
3.2	Comparative studies with concurrent controls and allocation not randomised [cohort studies], case-control studies, or interrupted time series with a control group
4	Case series, pre–test, and post–test, cross-sectional

There were four stages to searching, with stages 2-4 only undertaken if the highest level study type (i.e., level 1: systematic review of randomised controlled trials) was not identified in the previous stage. The hierarchy for selection of studies is detailed in Table 1. It should be noted that where narrative reviews were identified in stage 1 and 2, reference lists were searched for high-quality studies. Exclude study type 4.

Table 2. Hierarchy of searching for studies

Stage	Details
1	Cochrane Library of Systematic Reviews and EBM reviews search for Level 1 studies
2	Peer-reviewed literature database (Medline, Embase, PsycINFO) search for Level 1 studies
3	Peer-reviewed literature database (Medline, Embase, PsycINFO) search for Level 2-4 studies

Search Strategy

Cochrane Library of Systematic Reviews and EBM reviews (Full Text-Cochrane DSR, ACP Journal Club and DARE) search for Level 1 studies

The following searches were limited to those references published since 2000 and only Cochrane and CRD reviews.

Cochrane

	Search Group	Number of citations retrieved
1	opioid OR opiate OR heroin	16845
2	Limit 1 to "Cochrane reviews" and "2000-2018"	205

EBM

	Search Group	Number of citations retrieved
1	opioid.mp. [mp=title, short title, abstract, full text, keywords, caption text]	464
2	opiate.mp. [mp=title, short title, abstract, full text, keywords, caption text]	180
3	heroin.mp. [mp=title, short title, abstract, full text, keywords, caption text]	93
4	1 or 2 or 3	554
5	limit 4 to (full systematic reviews and last 18 years)	421

Peer-reviewed literature database searches for Level 1 studies

Medline search results

#	Terms	Results
1	heroin*.ti,ab.	11849
2	opiate*.ti,ab.	22313
3	opium*.ti,ab.	1687
4	opioid*.ti,ab.	64936
5	morphine*.ti,ab.	43307
6	exp opium/	1944
7	exp narcotics/	111411
8	exp heroin dependence/	8659
9	exp Heroin/	5251
10	exp opioid-related disorders/	22435
11	exp opiate alkaloids/	81411
12	exp analgesics, opioid/	103531
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	177000
14	exp intravenous drug abuse/	13925
15	injecting risk.ti,ab.	129
16	"IDU$1".tw.	5019
17	"IVDU$1".tw.	718
18	"PWID$1".tw.	718
19	"injecting drug".tw.	3694
20	"intravenous drug".tw.	7165
21	"injecting substance".tw.	9
22	"intravenous substance".tw.	56
23	exp substance abuse, intravenous/	13925
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	21532

#	Terms	Results
25	13 or 24	194862
26	exp intervention study/	790089
27	exp early intervention/	2495
28	drug dependence/di, dt, pc, rh, th [Diagnosis, Drug Therapy, Prevention, Rehabilitation, Therapy]	34941
29	exp substance abuse treatment centers/	5000
30	"drug dependence treatment".ti,ab.	100
31	exp harm reduction/	2347
32	Addiction/dt [Drug Therapy]	0
33	26 or 27 or 28 or 29 or 30 or 31 or 32	829093
34	(brief adj3 intervention).ti,ab.	3584
35	(safe adj3 inject*).ti,ab.	877
36	(needle adj2 syringe adj5 program).ti,ab.	66
37	exp condom/	9356
38	sexually transmitted disease/di, dt, pc, rh, th [Diagnosis, Drug Therapy, Prevention, Rehabilitation, Therapy]	12513
39	hepatitis C/di, dt, pc, rh, th [Diagnosis, Drug Therapy, Prevention, Rehabilitation, Therapy]	16277
40	Human immunodeficiency virus/pc [Prevention]	0
41	exp pre-exposure prophylaxis/	961
42	(prep adj5 HIV).ti,ab.	532
43	(prep adj5 sexual*).ti,ab.	72
44	(pre-exposure prophylaxis adj5 sexual*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	109
45	(drug adj3 consum* adj3 (room or facil*)).ti,ab.	25
46	(supervis* adj3 inject*).ti,ab.	226

#	Terms	Results
47	atypical antipsychotic agent/dt [Drug Therapy]	0
48	Suicide/pc [Prevention]	8402
49	(suicide adj3 prevent*).ti,ab.	4249
50	exp behavior therapy/	65237
51	exp motivational interviewing/	1222
52	exp cognitive therapy/	23038
53	"cognitive behavio?r therapy".ti,ab.	2635
54	exp self-help groups/	9629
55	((peer or mutual) adj3 support*).ti,ab.	3835
56	exp family therapy/	8414
57	multisystemic therapy.ti,ab.	156
58	exp therapeutic community/	2116
59	agonist pharmacotherap*.ti,ab.	22
60	(drug adj3 (compulsory or detention)).ti,ab.	95
61	"NSP$1".tw.	4021
62	"needle syringe program$".tw.	47
63	"NSEP$1".tw.	56
64	"needle syringe exchange program$".tw.	23
65	"needle exchange$1".tw.	871
66	"syringe exchange$1".tw.	569
67	exp Needle-Exchange Programs/	1551
68	exp Harm Reduction/	2347
69	"HAART".tw.	10467
70	"Anti?Retroviral Treatment".tw.	6218
71	"Anti?Retroviral Therapy".tw.	31258
72	"highly active anti?retroviral therapy".tw.	9978

#	Terms	Results
73	"highly active anti?retroviral treatment".tw.	491
74	"HIV treatment".tw.	3291
75	"anti-HIV Agents".tw.	757
76	"AIDS treatment".tw.	939
77	exp anti-hiv agents/	61737
78	exp hiv fusion inhibitors/	1136
79	exp hiv integrase inhibitors/	2139
80	exp hiv protease inhibitors/	12338
81	exp Antiretroviral Therapy, Highly Active/	19564
82	"OST".tw.	1066
83	"opioid substitution treatment".tw.	198
84	"methadone".tw.	11139
85	"MMT".tw.	1992
86	"methadone maintenance".tw.	3526
87	"buprenorphine".tw.	4856
88	"BMT".tw.	9731
89	"Buprenorphine maintenance".tw.	224
90	"opioid replacement".tw.	96
91	exp Buprenorphine/	4529
92	exp Methadone/	11561
93	exp Opiate Substitution Treatment/	2052
94	exp Buprenorphine, Naloxone Drug Combination/	190
95	"naltrexone".tw.	5769
96	"LAAM".tw.	293
97	"levomethadyl acetate".tw.	20
98	exp Naltrexone/	7339

#	Terms	Results
99	exp Methadyl Acetate/	406
100	"contingency management".tw.	754
101	Vaccine/dt [Drug Therapy]	0
102	"detoxification".ti,ab.	23495
103	"drug detoxification".ti,ab.	296
104	exp social support/	62877
105	exp rehabilitation centers/	13595
106	exp "acceptance and commitment therapy"/	216
107	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106	359004
108	33 or 107	1138477
109	exp Evaluation Studies/	233034
110	exp program evaluation/	67455
111	exp evidence based medicine/	67673
112	exp "Outcome Assessment (Health Care)"/	921018
113	exp patient outcome assessment/	4985
114	exp randomized controlled trial/	455867
115	random* controlled trial.ti,ab.	61699
116	exp Clinical Trials as Topic/	311580
117	exp controlled clinical trial/	543249
118	multicenter study/	230085
119	random*.ti,ab.	825940
120	(pretest or pre test).ti,ab.	13379
121	(posttest or post test).ti,ab.	13989

#	Terms	Results
122	before after.ti,ab.	3518
123	qua?irandomi*.ti,ab.	56
124	nonrandomi*.ti,ab.	9746
125	exp cohort analysis/	1720362
126	exp longitudinal study/	113428
127	exp Meta-Analysis as Topic/	16350
128	systematic review/	0
129	exp Clinical Trial/	790089
130	109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129	3593803
131	25 and 108 and 130	28470
132	limit 131 to (humans and yr="2000 -Current" and "review")	796

Searches conducted on 23/03/2018

Embase search results

#	Terms	Results
1	heroin*.ti,ab.	17939
2	opiate*.ti,ab.	31806
3	opium*.ti,ab.	2914
4	opioid*.ti,ab.	97282
5	morphine*.ti,ab.	64411
6	exp Diamorphine/	22857
7	exp Opiate/	69546
8	exp heroin dependence/	9183
9	exp opiate addiction/	14690
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	210638
11	exp intravenous drug abuse/	9784
12	injecting risk.ti,ab.	175
13	"IDU$1".tw.	7487
14	"IVDU$1".tw.	1189
15	"PWID$1".tw.	1307
16	"injecting drug".tw.	4753
17	"intravenous drug".tw.	9605
18	"injecting substance".tw.	10
19	"intravenous substance".tw.	72
20	exp substance abuse, intravenous/	49527
21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	72604
22	10 or 21	273105
23	exp intervention study/	35430
24	exp early intervention/	19363

#	Terms	Results
25	drug dependence/di, dm, dt, pc, rh, th [Diagnosis, Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy]	7797
26	exp drug dependence treatment/	19705
27	exp residential care/	11221
28	exp harm reduction/	4534
29	Addiction/dt [Drug Therapy]	1413
30	23 or 24 or 25 or 26 or 27 or 28 or 29	95877
31	(brief adj3 intervention).ti,ab.	5654
32	(safe adj3 inject*).ti,ab.	1489
33	(needle adj2 syringe adj5 program).ti,ab.	109
34	exp condom/	18629
35	sexually transmitted disease/di, dm, dt, pc, rh, th [Diagnosis, Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy]	12456
36	hepatitis C/di, dm, dt, pc, rh, th [Diagnosis, Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy]	38575
37	Human immunodeficiency virus/dm, pc [Disease Management, Prevention]	7
38	exp pre-exposure prophylaxis/	1660
39	(prep adj5 HIV).ti,ab.	996
40	(prep adj5 sexual*).ti,ab.	140
41	(pre-exposure prophylaxis adj5 sexual*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]	76
42	(drug adj3 consum* adj3 (room or facil*)).ti,ab.	35
43	(supervis* adj3 inject*).ti,ab.	351
44	atypical antipsychotic agent/ct, dt [Clinical Trial, Drug Therapy]	7690
45	Suicide/pc	5910
46	(suicide adj3 prevent*).ti,ab.	5886
47	exp behavior therapy/	42863

#	Terms	Results
48	exp motivational interviewing/	3338
49	exp cognitive behavioural therapy/	5043
50	exp self help/	12974
51	((peer or mutual) adj3 support*).ti,ab.	6276
52	exp family therapy/	12896
53	multisystemic therapy.ti,ab.	200
54	exp therapeutic community/	3051
55	agonist pharmacotherap*.ti,ab.	32
56	(drug adj3 (compulsory or detention)).ti,ab.	136
57	"NSP$1".tw.	5311
58	"needle syringe program$".tw.	75
59	"NSEP$1".tw.	81
60	"needle syringe exchange program$".tw.	33
61	"needle exchange$1".tw.	1078
62	"syringe exchange$1".tw.	725
63	exp preventive health service/	26240
64	"HAART".tw.	15971
65	"Anti?Retroviral Treatment".tw.	8878
66	"Anti?Retroviral Therapy".tw.	43929
67	"highly active anti?retroviral therapy".tw.	12656
68	"highly active anti?retroviral treatment".tw.	628
69	"HIV treatment".tw.	4851
70	"anti-HIV Agents".tw.	934
71	"AIDS treatment".tw.	1029
72	exp anti human immunodeficiency virus agent/	142530
73	exp human immunodeficiency virus fusion inhibitor/	12218

#	Terms	Results
74	exp highly active antiretroviral therapy/	35463
75	"contingency management".tw.	1075
76	Vaccine/dt [Drug Therapy]	5049
77	detoxification/	23238
78	exp drug detoxification/	4363
79	exp psychosocial care/	15876
80	exp residential care/	11221
81	exp rehabilitation center/	13384
82	exp cognitive therapy/	43099
83	exp "acceptance and commitment therapy"/	851
84	"OST".tw.	1946
85	"opioid substitution".tw.	788
86	"methadone".tw.	16914
87	"MMT".tw.	3538
88	"methadone maintenance".tw.	4772
89	"buprenorphine".tw.	7659
90	"Buprenorphine maintenance".tw.	337
91	"opioid replacement".tw.	155
92	"opioid agonist".tw.	3256
93	"opiate agonist".tw.	604
94	"opioid maintenance".tw.	497
95	"opiate maintenance".tw.	143
96	exp Buprenorphine/	14674
97	exp Methadone/	30108
98	exp Opiate Substitution Treatment/	1612
99	exp methadone treatment/	4162

#	Terms	Results
100	exp buprenorphine plus naloxone/	1297
101	"naltrexone".tw.	7969
102	exp Naltrexone/	13328
103	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102	531556
104	30 or 103	598139
105	exp evaluation study/	46728
106	exp program evaluation/	15815
107	exp evidence based medicine/	956745
108	exp outcome assessment/	411185
109	exp randomized controlled trial/	491232
110	random* controlled trial.ti,ab.	96486
111	"clinical trial (topic)"/	91565
112	exp controlled clinical trial/	669443
113	multicenter study/	177890
114	random*.ti,ab.	1287665
115	(pretest or pre test).ti,ab.	21706
116	(posttest or post test).ti,ab.	22682
117	before after.ti,ab.	6543
118	qua?irandomi*.ti,ab.	115
119	nonrandomi*.ti,ab.	12767
120	exp open study/	30572
121	exp cohort analysis/	350020
122	exp longitudinal study/	110258

#	Terms	Results
123	systematic review/	161232
124	"meta analysis (topic)"/	36687
125	105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124	2801496
126	22 and 104 and 125	11974
127	limit 126 to (human and yr="2000 -Current" and "review")	1823

Searches conducted on 21/03/2018

PsycINFO search results

#	Terms	Results
1	heroin*.ti,ab.	8779
2	opiate*.ti,ab.	8566
3	opium*.ti,ab.	592
4	opioid*.ti,ab.	19819
5	morphine*.ti,ab.	9991
6	exp Heroin addiction/	2489
7	exp Opiates/	22956
8	exp Heroin/	2556
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	39477
10	exp Intravenous Drug Usage/	3669
11	injecting risk.ti,ab.	107
12	"IDU$1".tw.	2123
13	"IVDU$1".tw.	119
14	"PWID$1".tw.	582
15	"injecting drug".tw.	1789
16	"intravenous drug".tw.	1022
17	"intravenous substance".tw.	13

#	Terms	Results
18	"injecting substance".tw.	5
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	5750
20	9 or 19	43797
21	exp intervention/	91049
22	exp early intervention/	9959
23	exp drug dependency/	24742
24	exp drug therapy/	134549
25	"drug dependence treatment".ti,ab.	87
26	exp harm reduction/	3131
27	exp Addiction/	56195
28	21 or 22 or 23 or 24 or 25 or 26 or 27	285287
29	(brief adj3 intervention).ti,ab.	3983
30	(safe adj3 inject*).ti,ab.	103
31	(needle adj2 syringe adj5 program).ti,ab.	66
32	exp condom/	3696
33	exp sexually transmitted disease/	42686
34	("Hepatitis C" or "HCV").ti,ab.	2737
35	exp HIV/	39644
36	(prep adj5 HIV).ti,ab.	221
37	(prep adj5 sexual*).ti,ab.	41
38	(pre-exposure prophylaxis adj5 sexual*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	8
39	(drug adj3 consum* adj3 (room or facil*)).ti,ab.	22
40	(supervis* adj3 inject*).ti,ab.	167
41	"atypical antipsychotic agent".ti,ab.	166
42	exp Suicide/	25670

#	Terms	Results
43	(suicide adj3 prevent*).ti,ab.	5599
44	exp behavior therapy/	18951
45	exp motivational interviewing/	2131
46	exp cognitive behavior therapy/	18032
47	exp self-help techniques/	9862
48	exp support groups/	5709
49	((peer or mutual) adj3 support*).ti,ab.	5910
50	exp family therapy/	21148
51	multisystemic therapy.ti,ab.	408
52	exp therapeutic community/	2741
53	agonist pharmacotherap*.ti,ab.	20
54	(drug adj3 (compulsory or detention)).ti,ab.	80
55	"NSP$1".tw.	359
56	"needle syringe program$".tw.	68
57	"NSEP$1".tw.	17
58	"needle syringe exchange program$".tw.	25
59	"needle exchange$1".tw.	509
60	"syringe exchange$1".tw.	404
61	exp preventive medicine/	2017
62	"HAART".tw.	1250
63	"Anti?Retroviral Treatment".tw.	954
64	"Anti?Retroviral Treatment".tw.	954
65	"Anti?Retroviral Therapy".tw.	4142
66	"highly active anti?retroviral therapy".tw.	1085
67	"highly active anti?retroviral treatment".tw.	68
68	"HIV treatment".tw.	1067

#	Terms	Results
69	"anti-HIV Agents".tw.	5
70	"AIDS treatment".tw.	248
71	"anti human immunodeficiency virus agent".ti,ab.	0
72	"human immunodeficiency virus fusion inhibitor".ti,ab.	0
73	"contingency management".tw.	1605
74	exp Immunization/	4076
75	detoxification/	1683
76	exp drug rehabilitation/	28677
77	exp psychosocial rehabilitation/	10810
78	exp rehabilitation centers/	1026
79	exp cognitive therapy/	12909
80	exp "acceptance and commitment therapy"/	1429
81	"OST".tw.	467
82	"opioid substitution".tw.	408
83	"methadone".tw.	7082
84	"MMT".tw.	786
85	"methadone maintenance".tw.	3421
86	"buprenorphine".tw.	2399
87	"Buprenorphine maintenance".tw.	213
88	"opioid replacement".tw.	58
89	"opioid agonist".tw.	951
90	"opiate agonist".tw.	142
91	"opioid maintenance".tw.	254
92	"opiate maintenance".tw.	57
93	exp Buprenorphine/	1588
94	exp Methadone/	1740

#	Terms	Results
95	"opiate substitution".ti,ab.	115
96	exp methadone maintenance/	3428
97	(buprenorphine and naloxone).ti,ab.	448
98	exp naltrexone/	1789
99	"naltrexone".tw.	3208
100	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99	217256
101	28 or 100	454618
102	exp treatment effectiveness evaluation/	22349
103	exp program evaluation/	19270
104	exp evidence based practice/	15874
105	"outcome assessment".ti,ab.	870
106	random* controlled trial.ti,ab.	16786
107	exp clinical trials/	10840
108	"controlled clinical trial".ti,ab.	1312
109	"multicenter study".ti,ab.	1362
110	random*.ti,ab.	175803
111	(pretest or pre test).ti,ab.	16361
112	(posttest or post test).ti,ab.	22005
113	before after.ti,ab.	820
114	qua?irandomi*.ti,ab.	12
115	nonrandomi*.ti,ab.	881
116	exp cohort analysis/	1248
117	exp longitudinal studies/	15918

#	Terms	Results
118	"systematic review".ti,ab.	19740
119	exp meta analysis/	4150
120	102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119	281942
121	20 and 101 and 120	2986
122	limit 121 to (human and "reviews (best balance of sensitivity and specificity)" and yr="2000 -Current")	1669

Searches conducted on 27/03/2018

Table 3. Grades of evidence

Grade	Evidence
A	Consistent conclusions across meta-analyses, high quality systematic reviews of randomised controlled trials, or several randomised controlled trials
B	Evidence from one or two randomised controlled trials only
C	High-quality systematic reviews with some inconsistent conclusions from authors, or several consistent ecological studies or cohort studies
D	Cross-sectional association, case series suggesting outcome, or a single cohort study

Description of evidence on reviews of interventions to reduce health outcomes

Opioid Agonist Treatment (OAT)

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
All-cause mortality	Mattick	2014	?	0.48	0.1	2.39	RR	Systematic review and MA of RCTs	4		Moderate quality evidence
All-cause mortality	Sordo	2017	↓					Systematic review and MA of cohort studies	19		noted potential for confounding and selection bias as all cohorts
All-cause mortality	Crowley	2017	↓					Systematic review of RCTs and other study designs	Eight randomised control trials (RCT), one non-randomised trial and five observational studies	taken from abstract, could not access paper	
All-cause mortality	Ayanga	2016	?					Review (methods unclear)		referred to Mattick et al Cochrane reviews	
Contact with the criminal justice system	Perry	2015	×	0.6	0.32	1.14	RR	Systematic review and MA of RCTs	1	arrest	Low quality evidence
Contact with the criminal justice system	Perry	2015	×	0.77	0.36	1.64	RR	Systematic review and MA of RCTs	3	reincarceration	Low quality evidence
Contact with the criminal justice system	Maglione	2018	×	0.75	0.46	1.23	RR	Systematic review and MA of RCTs and cohort studies	6	arrest or incarceration	
Criminal activity	Mattick	2014	×	0.39	0.12	1.25	RR	Systematic review and MA of RCTs	3	any criminal activity	Moderate quality evidence
Criminal activity	Ayanga	2016	?					Review (methods unclear)		referred to Mattick et al Cochrane reviews	
Criminal activity	Perry	2015	↓	-74.2	-133.5	-14.89	MD	Systematic review and MA of RCTs	1	criminal activity continuous	Low quality evidence
Criminal activity	Maglione	2018	↓	-0.57	-1.00	-0.13	SMD	Systematic review and MA of RCTs and cohort studies	2	criminal activity continuous	
HCV incidence	Connery	2015	↓					Systematic review of RCTs and cohort studies	unclear		
HCV incidence	Hagan	2012	x	0.60	0.35	1.03	RR	Systematic review and MA of cohort studies	8		No information on quality of evidence
HCV incidence	MacArthur	2014	↓					Review of reviews			There is tentative review-level evidence to support the effectiveness of OST in reducing HCV transmission
HCV incidence	Platt	2017	↓	0.50	0.40	0.63	RR	Systematic review and MA of cohort studies	21		Low quality evidence
HIV incidence	Gowing	2011	↓					Systematic review and MA of RCTs and cohort studies	4		
HIV incidence	Connery	2015	↓					Systematic review of RCTs and cohort studies	unclear		
HIV incidence	MacArthur	2012	↓	0.46	0.32	0.67	RR	Systematic review and MA of cohort studies	9		
HIV incidence	MacArthur	2014	↓					Review of reviews			There is sufficient review-level evidence to conclude that OST is effective in reducing HIV seroconversion
HIV linkage to care and treatment	Low	2016	↑	1.54	1.17	2.03	OR	Systematic review and MA of cohort studies	10	Odds of being on HIV therapy	
HIV linkage to care and treatment	Low	2016	↑	1.87	1.50	2.33	HR	Systematic review and MA of cohort studies	4	Effect of OST on initiating HIV therapy	
HIV treatment adherence	Low	2016	↑	2.14	1.41	3.26	OR	Systematic review and MA of cohort studies	5	Effect of OST on adherence to HIV therapy	
HIV viral suppression	Low	2016	↑	1.45	1.21	1.73	OR	Systematic review and MA of cohort studies	10	Effect of OST on HIV viral load suppression	
Injecting frequency	Gowing	2011	↓	-0.59	-0.91	-0.26	SMD	Systematic review and MA of RCTs and cohort studies	10	we have pooled estimates - Gowing did not - RCTs	
Injecting risk behaviour	Gowing	2011	↓	0.53	0.4	0.7	RR	Systematic review and MA of RCTs and cohort studies	12	we have pooled estimates - Gowing did not - RCTs	
Injecting risk behaviour	Connery	2015	↓					Systematic review of RCTs and cohort studies	unclear		
Injecting risk behaviour	Macarthur	2014	↓					Review of reviews			In light of primary evidence and statements of evidence from core reviews in support of OST, we concluded that there is sufficient evidence to support effectiveness of OST in reducing IRB.
Mental health	Fingleton	2015	↑					Systematic review of RCTs and cohort studies	19 RCTs and 3 cohorts	varied assessment of mental health across studies	
Mental health	Maglione	2018	×					systematic review	3	differing measurements; ASI and SF-12	
Mental health	Feelmeyer	2014	↑	0.491	0.351	0.631	SMD	Systematic review and MA of cohort studies	8 with 9 samples	Clients in OST in low and middle income countries; used WHOQOL-BREF and ASI - reported separately by different domains; this one is psychological	
Neonatal outcomes	Tran	2017						Systematic review of RCTs and other study designs	3 RCTs and 8 observational studies	birth weight - all methadone vs. bupe	
Neonatal outcomes	Tran	2017						Systematic review of RCTs and other study designs	3 RCTs and 8 observational studies	neonatal abstinence syndrome - all methadone vs. bupe	
Neonatal outcomes	Minozzi	2013	↑	-365	-673	-57	MD	Systematic review and MA of RCTs	2	birth weight	Low quality evidence
Neonatal outcomes	Minozzi	2013	×	1.22	0.89	1.67	RR	Systematic review and MA of RCTs	3	number treated for neonatal abstinence	Very low quality evidence
Neonatal outcomes	Minozzi	2013	×	0	-0.03	0.03	MD	Systematic review and MA of RCTs	2	APGAR score	Very low quality evidence

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
Neonatal outcomes	Hand	2017						Review (methods unclear)			
Neonatal outcomes	Zedler	2016	↑	0.40	0.18	0.91	RR	Systematic review and MA of RCTs and cohort studies	This outcome had 2 RCTs; overall review had Three RCTs (n = 223) and 15 cohort OBSs (n = 1923) - have extracted RCT only	pre-term birth	Low quality evidence
Neonatal outcomes	Zedler	2016	↑	324	32	617	RCT WMD	Systematic review and MA of RCTs and cohort studies	This outcome had 2 RCTs; overall review had Three RCTs (n = 223) and 15 cohort OBSs (n = 1923) - have extracted RCT only	birth weight	Low quality evidence
Neonatal outcomes	Zedler	2016	↑	0.90	0.14	1.66	RCT WMD	Systematic review and MA of RCTs and cohort studies	This outcome had 2 RCTs; overall review had Three RCTs (n = 223) and 15 cohort OBSs (n = 1923) - have extracted RCT only	head circumference	Low quality evidence
Neonatal outcomes	Noormohammadi	2016						Systematic review of RCTs and other study designs	5 studies		
Neonatal outcomes	Holbrook	2015						Review of reviews	9 reviews and one MA		
Opioid use	Mattick	2014	↓	0.66	0.56	0.78	RR	Systematic review and MA of RCTs	6	morphine positive urine or hair	High quality evidence
Opioid use	Mattick	2014	↓				RR	Systematic review and MA of RCTs	6	self-reported heroin use	High quality evidence
Opioid use	Nielsen	2016	↓	0.63	0.43	0.91	RR	Systematic review and MA of RCTs	3	morphine positive urine or hair	Low quality evidence
Opioid use	Nielsen	2016	↓	0.54	0.31	0.93	RR	Systematic review and MA of RCTs	3	self-reported opioid use	Low quality evidence
Opioid use	Gowing	2011	↓	0.48	0.41	0.55	RR	Systematic review and MA of RCTs and cohort studies	11	we have pooled estimates from follow-up studies	
Opioid use	Ayanga	2016	↓					Review (methods unclear)		referred to Mattick et al Cochrane reviews	
Opioid use	Thomas	2015	↓					Systematic review of reviews, MAs, RCTs and cohort studies	7 reviews or MAs, 16 RCTs, a randomized cross-over study, a study using a self-administered survey, and a retrospective descriptive study		High quality evidence
Overdose mortality	Sordo	2017	↓					Systematic review and MA of cohort studies	19		noted potential for confounding and selection bias as all cohorts
Overdose mortality	Connery	2015	↓					Systematic review of RCTs and cohort studies	unclear		
Overdose mortality	Ma	2018	↓	0.12	0.06	0.22	RR	Systematic review and MA of cohort studies	6	in treatment vs. untreated	
Overdose mortality	Ma	2018	↓	0.32	0.25	0.42	RR	Systematic review and MA of cohort studies	14	in treatment versus out of treatment	
Quality of life	Fei	2016	↑					Retrospective cohort		Cohort of patients retained in treatment in Malaysia	
Quality of life	Feelmeyer	2014	↑	0.292	0.164	0.421	SMD	Systematic review and MA of cohort studies	8 with 9 samples	Clients in OST in low and middle income countries; used WHOQOL-BREF and ASI - reported separately by different domains; this one is social	
Quality of life	Maglione	2018	↑								
Quality of life	Thornton	2017	X	-0.05	-0.18	0.08	Hedge's G effect size	Systematic review	3	people receiving long term opioid therapy for pain - mental component summary score	
Quality of life	Thornton	2017	↑	0.18	0.08	0.28	Hedge's G effect size	Systematic review	3	people receiving long term opioid therapy for pain - physical component summary score	
Skin and soft tissue infections	Larney	2017	?					Systematic review	3	all cross-sectional studies assessing whether past year or ever OST associated with past 6-12 month abscesses	

OAT vs. no treatment

Overdose

Table J1. Calculated overdose deaths rate ratios using data identified in Sordo, 2017 and Hickman, 2019

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Buster, 2002	0.946	0.567	1.608	8.92
Caplehorn, 1996	0.235	0.058	0.708	4.75
Clausen, 2008	0.173	0.097	0.310	8.51
Cousins, 2016	0.601	0.377	1.050	8.97
Cushman, 1977	0.103	0.022	0.403	3.96
Davoli, 2007	0.135	0.043	0.407	5.31
Gearing, 1974	0.127	0.071	0.231	8.49
Grönbladh, 1990	0.177	0.065	0.416	6.36
Hickman, 2018 (methadone)	0.422	0.252	0.699	8.99
Hickman, 2018 (buprenorphine)	0.319	0.090	0.938	5.10
Kimber, 2015 (methadone)	0.386	0.314	0.474	10.56
Kimber, 2015 (buprenorphine)	0.309	0.202	0.458	9.60
Peles, 2010	0.070	0.020	0.210	5.04
Scherbaum, 2002	0.071	0.022	0.201	5.44
Pooled rate ratio	0.253	0.176	0.363	100.00

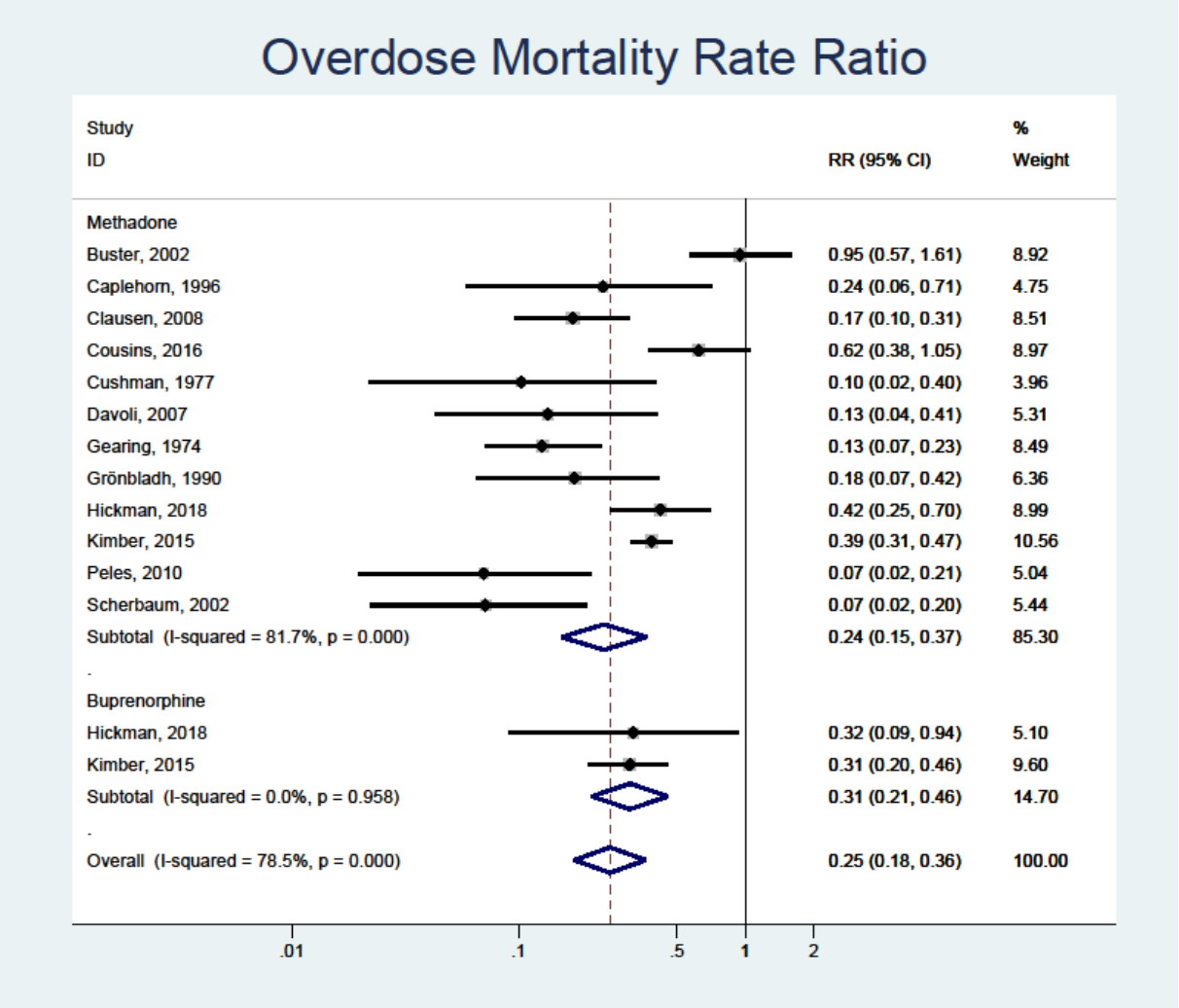

Figure J1. Pooled rate ratio of overdose deaths within buprenorphine/methadone treatment vs. no treatment (ref) as calculated using data within Sordo, 2017 and Hickman, 2018.

All-cause mortality

Table J2. Calculated all-cause mortality rate ratios using data identified in Sordo, 2017

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Caplehorn, 1996	0.353	0.162	0.708	3.05
Clausen, 2008	0.395	0.274	0.577	5.67
Cornish, 2010 (methadone)	0.353	0.222	0.548	4.98
Cornish, 2010 (buprenorphine)	0.710	0.230	2.068	1.74
Cousins, 2016	0.324	0.245	0.428	6.51
Cushman, 1977	0.320	0.160	0.667	3.18
Degenhardt, 2009	0.407	0.370	0.446	7.82
Evans, 2015	0.366	0.308	0.433	7.38
Fugelstad, 1995	0.298	0.086	1.156	1.32
Fugelstad, 1998	0.564	0.143	2.625	1.09
Fugelstad, 2007	0.407	0.292	0.567	6.03
Gearing, 1974	0.269	0.181	0.411	5.34
Grönbladh, 1990	0.341	0.175	0.640	3.55
Hickman, 2018 (methadone)	0.357	0.212	0.585	7.30
Hickman, 2018 (buprenorphine)	0.305	0.254	0.366	4.53
Kimber, 2015 (methadone)	0.557	0.497	0.625	7.72
Kimber, 2015 (buprenorphine)	0.395	0.308	0.502	6.80
Nosyk, 2015	0.172	0.132	0.221	6.70
Peles, 2010	0.147	0.096	0.226	5.18
Reece, 2010	0.463	0.092	1.454	1.19
Scherbaum, 2002	0.199	0.093	0.431	2.91
Pooled rate ratio	0.334	0.284	0.394	100.00

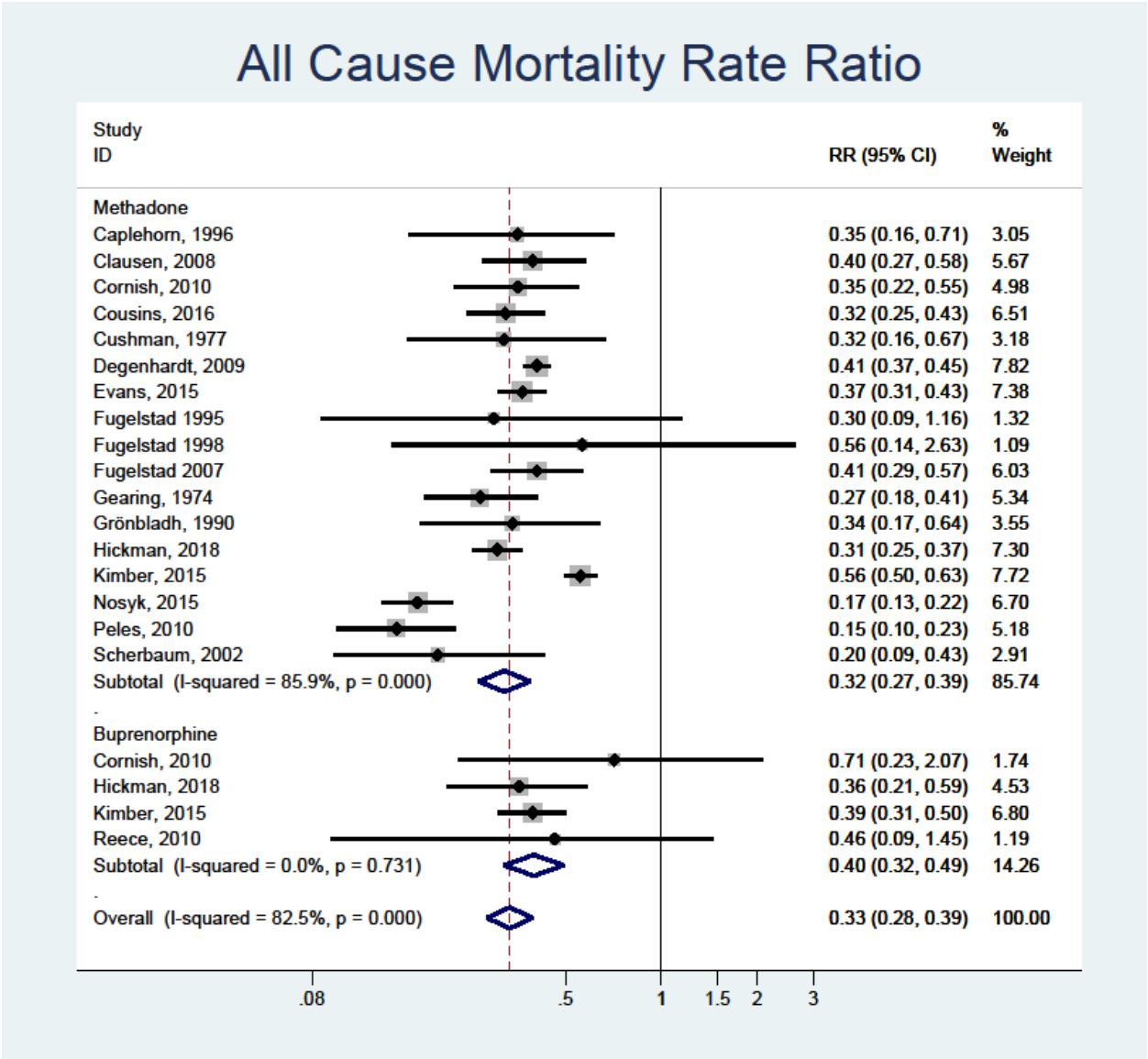

Figure J2. Pooled rate ratio of all-cause mortality within buprenorphine/methadone treatment vs. no treatment (ref) using calculated rate ratios from data within Sordo, 2017 and Hickman, 2018.

Systematic reviews of OAT versus no treatment in prison

Outcome examined	First author	Year	Impact	Effect	95 % CI	95 % CI	Author notes on quality of evidence
Opioid use	Hedrich	2012	↓				
Injecting risk behaviour	Hedrich	2012					
HIV incidence	Hedrich	2012	?				insufficient evidence
HCV incidence	Hedrich	2012	?				insufficient evidence
Opioid use	Larney	2010	↓				
Injecting risk behaviour	Larney	2010	↓				
HIV incidence	Larney	2010	?				no evidence

Buprenorphine vs. methadone (ref)

Overdose during induction (4 weeks)

Table J3. Overdose deaths rate ratios within first 4 weeks of treatment

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Hickman, 2018	0.240	0.030	1.960	42.78
Kimber, 2015	0.177	0.020	0.741	57.22
Pooled rate ratio	0.202	0.051	0.792	100.00

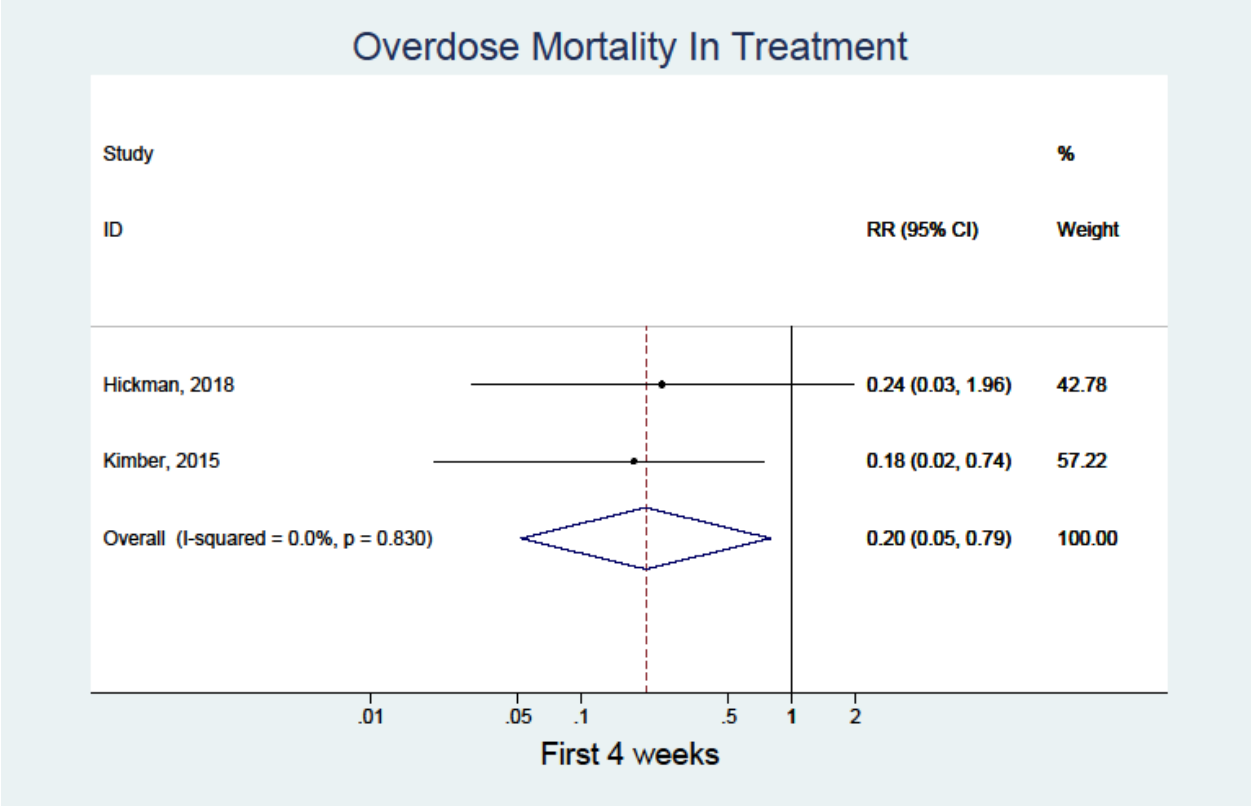

Figure J3. Pooled rate ratio of overdose deaths within first 4 weeks of treatment.

Overdose following cessation (4 weeks)

Table J4. Overdose death rate ratios within first 4 weeks out of treatment

Study	Rate ratio	95% confidence interval		% Weight
		Lower	Upper	
Hickman, 2018	1.170	0.460	2.970	45.73
Kimber, 2015	1.974	0.864	4.787	54.27
Pooled rate ratio	1.554	0.827	2.920	100.00

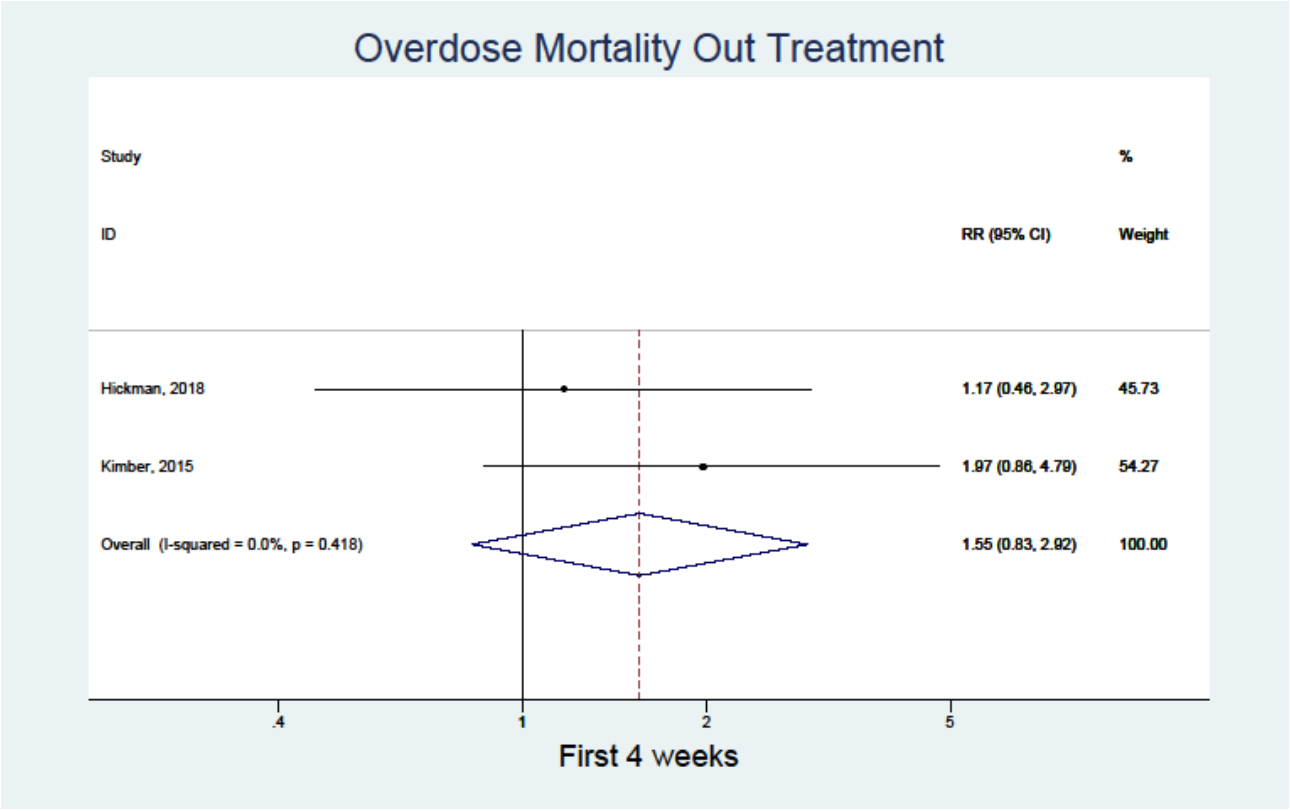

Figure J4. Pooled rate ratio of overdose deaths within first 4 weeks out of treatment.

Panel J1 – Other opioid agonist treatments (OAT) for opioid dependence

Injectable opioids are prescribed in a small number of countries for the treatment of opioid dependence refractory to oral opioid substitution treatment. Diamorphine (pharmaceutical heroin) is the most widely prescribed injectable opioid, currently used to treat opioid dependence in the United Kingdom, Denmark, Germany, the Netherlands, Switzerland, and Canada. Injectable doses of diamorphine are taken under direct medical or nursing supervision.

A recent systematic review of supervised injectable diamorphine for the treatment of opioid dependence identified six randomised controlled trials.[62] The comparator in each trial was oral methadone, with some studies including an additional comparator. A meta-analysis suggested significantly better retention in injectable diamorphine compared to oral methadone (RR 1.37; 95%CI 1.03–1.83). Extra-medical opioid use was measured differently across trials, precluding meta-analysis, but all five of the trials to examine this outcome reported a significantly greater suppression of illicit heroin use with injectable diamorphine compared to oral methadone.

The Randomised Injectable Opiate Treatment Trial (RIOTT) was a three-arm randomised controlled trial comparing injectable diamorphine, injectable methadone, and optimised oral methadone (daily doses of >80mg with psychosocial support). Injectable diamorphine was superior to injectable and oral methadone at suppressing illicit heroin use; injectable methadone was not superior to oral methadone in suppressing illicit heroin use.[63]

Injectable hydromorphone was compared to injectable diamorphine in the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) study. Non-inferiority of injectable hydromorphone to injectable diamorphine in suppressing illicit opioid use was confirmed.[64] Injectable hydromorphone is offered alongside injectable diamorphine as a treatment option in Vancouver, British Columbia.[65]

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Panel J2 – Improving opioid agonist treatment access, retention and outcomes

There are many opportunities to improve the quality of care provided in OAT. Key barriers to treatment entry include: lack of unsupervised dosing, extensive assessment processes, delays to treatment following presentation, mandatory engagement in psychosocial counselling, siloing of OAT in specialist clinics, and geographically distant clinics and pharmacies for medication delivery.

In many countries, there is a requirement for official registration of a patient due to the scheduling of opioid medications. This information can sometimes be shared with police (either by law, or in practice), and clients may be targeted by police, lose their driver's license, experience restrictions on employment, and other adverse consequences[1,2].

Opportunities to improve OAT access, retention and outcomes:

- Rapid access to OAT with minimal assessment to establish opioid dependence in several settings such as emergency rooms, community-based settings, primary care and criminal justice settings
- OAT prescribing in a range of settings, beyond specialised settings including primary care, and OAT dispensing in community pharmacies
- Elimination of compulsory counselling requirements (e.g. in the US); instead, make provision of psychosocial services that may be accessed on a voluntary basis
- Minimise intensity of care as people stabilise in treatment (e.g., transition to less supervision as patients become clinically stable)
- Increased and rapid access to unsupervised dosing, particularly for people prescribed buprenorphine or stabilised on methadone
- Minimise use of urine drug screening; use results of such screening to improve care (i.e. dose adjustment) rather than to terminate treatment
- Low-threshold and adapted care for disengaged individuals, such as those who are homeless or with mental health issues (e.g., many required assessments can be obtained after starting OAT)
- Access to alternative agonist treatments such as slow release oral morphine and injectable opioid agonist therapy for individuals who do not respond to methadone or buprenorphine

References

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Provision of sterile injecting equipment

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes o
HCV incidence	Fernandes	2017						Review of reviews			
HCV incidence	Hagan	2012	↑	1.62	1.04	2.52	RR	Systematic review and MA of cohort studies	7	Volunteer bias in studies which found an association between HCV acquisitio PWID	
HCV incidence	Turner	2011	↓	0.48	0.25	0.93	aOR	Individual participant data meta-analysis	3	Evaluated high NSP coverage (>=100%) compared to <100%	
HCV incidence	MacArthur	2014	?					Review of reviews			Insufficient evic
HCV incidence	Platt	2017	x	0.77	0.38	1.54	RR	Systematic review and MA of cohort studies	10	Overall (NA + Europe)	
HCV incidence	Platt	2017	↓	0.44	0.24	0.80	RR	Systematic review and MA of cohort studies	6	Europe alone	
HCV incidence	Platt	2017	x	1.58	0.57	4.42	RR	Systematic review and MA of cohort studies	3	NA alone	
HCV incidence	Sawangijit	2017	?					Systematic review and meta-analysis		review of pharmacy-based NSP	Insufficient evic
HIV incidence	Fernandes	2017	↓					Review of reviews			
HIV incidence	Aspinall	2014	↓	0.66	0.43	1.01	OR/HR/RR	Systematic review and MA of cohort studies	12	Across all studies	
HIV incidence	Aspinall	2014	↓	0.42	0.22	0.81	OR/HR/RR	Systematic review and MA of cohort studies	6	Higher quality studies (according to Newcastle-Ottawa tool)	
HIV incidence	MacArthur	2014	↓					Review of reviews			
HIV incidence	Sawangijit	2017	?					Systematic review and meta-analysis		review of pharmacy-based NSP	Insufficient evic
Injecting risk behaviour	Turner	2011	↓	0.52	0.32	0.83	aOR	Individual participant data meta-analysis		Evaluated high NSP coverage (>=100%)	
Injecting risk behaviour	Fernandes	2017						Review of reviews			
Injecting risk behaviour	MacArthur	2014	↓					Review of reviews	43		Sufficient evide
Injecting risk behaviour	Sawangijit	2017	↓	0.5	0.34	0.73	OR	Systematic review and meta-analysis		review of pharmacy-based NSP	
Skin and soft tissue infections	Larney	2017	?					Systematic review	3	all cross-sectional studies assessing whether past year or current NSP associa	

Naloxone

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes
Non-fatal overdose	McAuley	2015	?	9.2	5.2	13.1	users per 3 months per 100 PWID		25	uses per 100 PWID trained and given naloxone; estimated 40 uses per 100 PWID trained per year, but 9.2*4 = 37
Non-fatal overdose	Clark	2014	?	-						
	Mueller	2015	↓	-						examined cohort studies

Drug consumption rooms (DCRs)

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
Non-fatal overdose	Potier	2014	↓					Systematic review that located a simulation study, ITS, cross-sectional survey	3		
Overdose mortality	Potier	2014	↓					Systematic review that located an ITS study	1		
Injecting risk behaviour	Potier	2014	↓					Systematic review that located a MA, a cross-sectional survey	4		
Skin and soft tissue infections	Potier	2014	?				incidence	Systematic review that located three papers on the SEOSI cohort	3	3 papers examining SEOSI cohort, mentions no evidence for 'viral transmission ' in the same paragraph. Is it worth doing a '?' for each of HIV incidence, HICv incidence, etc.	
Injecting risk behaviour	Milloy	2009	↓	0.31	0.17	0.55	RR	MA of three cohorts	3	Look at sharing, lending and borrowing needles. Sep. info for HIV negative and positive	
Skin and soft tissue infections	Larney	2017	↓	0.47	0.23	0.94	OR	Systematic review	1	1 cross-sectional study, Unadjusted, 'Current-1 month'	
Injecting risk behaviour	Macarthur	2014	↓					Review of reviews		statement of insufficient evidence from a core review, tentative statements of evidence from two supplementary reviews, and evidence from a number of robust studies	Tentative review-level evidence that injecting risks decrease
HIV incidence	Macarthur	2014	?					Review of reviews	1 cross-sectional study identified across reviews		Insufficient evidence to either support or discount the effectiveness of SIFs in preventing HIV
HCV incidence	Macarthur	2014	?					Review of reviews	1 cross-sectional study identified across reviews		Insufficient evidence to either support or discount the effectiveness of SIFs in preventing HCV

Oral opioid antagonists

Outcome examined	First author	Year	Journal	Title	Impact	Effect	95 % CI	95 % CI	Measure	Level of evidence	Number of studies in review	Notes
Contact with the criminal justice system	Maglione	2018	Journal of Substance Abuse Treatment	Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review	x				MD	systematic review	1	number of charges or number of arrests reported
Opioid use	Jahagirdar, D.	2017	CADTH evidence review	Naltrexone for Opioid Use Disorders: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines	X					systematic review		Ten randomized controlled trials13-22 and four systematic reviews were included in the review.23-26 Two of the trials were pilot/proof-of-concept studies.18,19 One study14 was a SUMMARY WITH CRITICAL APPRAISAL Naltrexone for Opioid Use Disorders 6 secondary analysis of data from a trial that was also included in this report.13 Three of the systematic reviews included both randomized controlled trials and observational

												studies, and included two,23 six24 and four25 studies of naltrexone respectively. The last systematic review included thirteen randomized or controlled clinical trials on oral naltrexone.26 The most recent systematic review included publications until December 2016,24 while the others included literature up to December 2009,25 June 2010,26 and September 2009.23
Opioid use	Minozzi	2011	John Wiley & Sons, Ltd	Oral naltrexone maintenance treatment for opioid dependence	x		1.39	0.61	3.17	abstinence	systematic review	

Sustained release opioid antagonists

Outcome examined	First author	Year	Journal	Title	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes
Contact with the criminal justice system	Maglione	2018	Journal of Substance Abuse Treatment	Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review	↓	-0.23	-0.46	-0.01	SMD	Systematic review	1 RCT	mean number of arrest at 78 weeks
Opioid use	Larney	2014	Drug and Alcohol Review	Systematic review of naltrexone implants for opioid dependence	↓	0.57	0.48	0.68	RR	systematic review and MA where possible	5 RCTs	compared to placebo; no difference cf. TAU
Non-fatal overdose	Larney	2014	Drug and Alcohol Review	Systematic review of naltrexone implants for opioid dependence	?					systematic review	2 RCTs, 1 non-RCT	no difference from oral naltrexone or treatment as usual
All-cause mortality	Larney	2014	Drug and Alcohol Review	Systematic review of naltrexone implants for opioid dependence	?					systematic review and MA where possible	4 RCTs, 3 non-RCTs	
Opioid use	Jahagirdar, D.	2017	CADTH evidence review	Naltrexone for Opioid Use Disorders: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines	↓						Ten randomized controlled trials and four systematic reviews	
Non-fatal overdose	Jarvis	2018			↓?					systematic review and MA where possible		no overdoses noted; comparative analysis not possible

Residential rehabilitations

Outcome examined	First author	Year	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review
Opioid use	Malivert	2012	↓					prospective and retrospective studies	12

HIV testing and informing of serostatus

Outcome examined	First author	Year	Impact
Injecting risk behaviour	Schlumberger	1999	↓

HCV testing and informing of serostatus

Outcome examined	First author	Year	Impact	Effect	95 % CI	95 % CI	Measure	Level of evidence	Number of studies in review	Notes
Injecting drug use	Spelman	2015	↓	0.95	0.93	0.96	aOR	Merged cohort study analysis	NA	HCV-positive diagnosed PWID demonstrated a 5% per 3-month reduction post-notification in the odds of recent injection drug use
Injecting risk behaviour	Spelman	2015	X	0.97	0.94	1.00	aOR	Merged cohort study analysis	NA	HCV-positive diagnosed PWID demonstrated a 3% per 3-month reduction post-notification in the odds of receptive syringe sharing

HIV treatment

Outcome examined	First author	Year	Journal	Title	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes
Injecting risk behaviour	Wood	2012	Current opinion in HIV and AIDS	HIV treatment as prevention among injection drug users	X						3	all cohort studies; no quantitative synthesis and two very old studies
Injecting risk behaviour	Kuyper	2011	Addictive Behaviors	Does initiation of HIV antiretroviral therapy influence patterns of syringe lending among injection drug users?	X	0.87	0.42	1.45	aOR		1	1 cohort study

HCV treatment

Suicide prevention strategies

Outcome examined	First author	Year	Title					Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
Suicide	Hawton	2015	?					Systematic review of RCTs		7		studies of people with history of self-harm			low to very low evidence; not possible to make a firm conclusion	

Limits on opioid prescribing

n/a

Prescription opioid monitoring programmes

Outcome examined	First author	Year	Journal	Title	Impact	Effect	95% CI	95% CI	Measure	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
Non-fatal overdose	Fink	2018	Annals of Internal Medicine	Association between prescrpition drug monitoring programmes and nonfatal and fatal drug overdoses	?					Systematic review	3	Authors noted serious risk of bias in studies	Low strength evidence - evidence is "insufficient" to make a conclusion
Overdose mortality	Fink	2018	Annals of Internal Medicine	Association between prescrpition drug monitoring programmes and nonfatal and fatal drug overdoses	?					Systematic review	10	Authors noted serious risk of bias in studies	Low strength evidence - evidence is "insufficient" to make a conclusion

Abuse-deterrent opioids

Outcome examined	First author	Year	Impact	Level of evidence	Number of studies in review	Notes	Author notes on quality of evidence
All-cause mortality	ICER	2017	?	Systematic review	6	all ecological studies; specific drug declined but on consistent trends in overall - unclear if overall impact, other opioids increased	"extremely mixed" "limited evidence" "no ocnisstent trends across studies"
Opioid use	ICER	2017	?	Systematic review	16	pre/post studies of poison centre data (3), treatment entrants (6)and cohorts (3)	evidence is "mixed" for opioid "abuse"

Compulsory drug detention centres

Werb D, Kamarulzaman A, Meacham MC, et al. The effectiveness of compulsory drug treatment: A systematic review. The International journal on drug policy 2016; 28: 1-9.

Criminalisation of drug use

DeBeck K, Cheng T, Montaner JS, et al. HIV and the criminalisation of drug use among people who inject drugs: a systematic review. The Lancet HIV 2017; 4(8): e357-e74.

Table J5: Current evidence for effects of interventions to address key outcomes and behaviours among people who use opioids extra-medically

Intervention	Injecting risk behaviours				Extra-medical opioid use				HIV incidence				HCV incidence				Skin and soft tissue infections				Quality of life			
	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources
Provision of sterile injecting equipment	↓	aOR 0.52 (0.32, 0.83)	A[PWID]	1	-	-	-	-	↓	OR/HR/RR 0.42 (0.22, 0.81)	C[PWID]	2	↓?	RR 0.77 (0.38, 1.54)	C	3	?	-	D	4	-	-	-	-
Condom provision	-	-	-	-	-	-	-	-	↓	RR 0.29, (0.20, 0.43)	A[GEN]	5	?	-	C	6	-	-	-	-	-	-	-	-
Naloxone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drug consumption rooms	↓	RR 0.31 (0.17, 0.55)	C[PWID]	7	-	-	-	-	?	-	D	8	?	-	D	8	↓	OR 0.47 (0.23, 0.94)	E	4	-	-	-	-
Peer-based self-help groups	-	-	-	-	↓?	-	B[ALC]	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosocial interventions	↓	SMD -0.43 (-0.69, -0.18)	A	10	↓	WMES -0.18 (-0.30, -0.06)	A	11	?	-	D	8	?	-	D	8	?	-	E	12	-	-	-	-
Opioid detoxification alone					✕																			
Oral opioid antagonists	✕	NE	A	13	✕	RR 1.39 (0.61, 3.17)	A	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Extended-release opioid antagonists	↓	NE	A	15	↓	NE	A	15,16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Opioid agonist treatment	↓	RR 0.53 (0.4, 0.7) SYNTH	A	17	↓	RR 0.48 (0.41, 0.55) SYNTH	A	17	↓	RR 0.46 (0.32, 0.67)	C	18	↓	RR 0.50 (0.40, 0.63)	C	3	?	-	D	4	↑	SMD 0.29 0.16, 0.42)	C	19
Residential rehabilitation	↓	NE	C	20	↓	NE	C	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV testing + informing of serostatus	↓	NE	D[PWID]	21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV testing + informing of serostatus	✕	aOR 0.97 (0.94, 1.00)	C[PWID]	22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV treatment	✕	aOR 0.78 (0.42-1.45)	D	23	-	-	-	-	↓	-	D	24	-	-	-	-	-	-	-	-	-	-	-	-
HCV treatment	↓	NE	D[PWID]	25	↓	NE	D[PWID]	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STI treatment	-	-	-	-	-	-	-	-	↓		A[GEN]	26-28	-	-	-	-	-	-	-	-	-	-	-	-
Suicide prevention strategies	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Opioid prescribing limits	-	-	-	-	↓?	NE	D[GEN]	29	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Abuse-deterrent opioid formulations	↓	NE	D	30,31	?	NE	D	31	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prescription opioid monitoring programs	-	-	-	-	↓?	NE	D[GEN]	29,32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Compulsory drug treatment/drug detention centres	↑	NE	C*	33,34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Criminalisation of drug use	↑	NE	C[PWID]	35					↑	NE	C[PWID]	35												

Notes on codes used in this table

Presence or absence of effect

✕ This intervention does not appear to have a significant effect upon the outcome
↑ This outcome may be increased by the intervention
↓This outcome is decreased by the intervention
- No evidence could be located of the impact of this intervention upon the outcome
? unclear evidence on impact of this intervention on the outcome

Level of evidence

A Consistent conclusions across meta-analyses, high quality systematic reviews, or multiple randomised controlled trials
B Evidence from one or two randomised controlled trials only
C High quality systematic reviews of cohort, case-control or cross-sectional studies
D Systematic reviews with inconsistent conclusions from authors or cross-sectional; OR multiple consistent ecological studies
E Cross-sectional association, case series suggesting outcome, single cohort study
GEN Evidence drawn from people who may not specifically use any drugs (including opioids)
PWID People who inject drugs that may not include opioids
ALC Note that this evidence pertains to people attending alcoholics anonymous
NE no pooled quantitative estimate reported

Intervention	Overdose				Suicide				Other injuries				Overall mortality			
	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources	Effect	Size of effect	Level	Sources
Provision of sterile injecting equipment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Condom provision	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Naloxone	↓	-	D	36	-	-	-	-	-	-	-	-	-	-	-	-
Drug consumption rooms	↓	-	D	37	-	-	-	-	-	-	-	-	-	-	-	-
Peer-based self-help groups	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosocial interventions	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Opioid detoxification alone																
Oral opioid antagonists	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Extended-release opioid antagonists	↓?	-	A	15	-	-	-	-	-	-	-	-	?	-	A	15,16
Opioid agonist treatment	↓	RaRa 0.25 (0.18, 0.36) SYNTH	C	38	↓	RaRa 0.48 (0.39, 0.59)	E	39	↓	RaRa 0.40 (0.34, 0.46)	E	39	↓	RaRa 0.33 (0.28, 0.39) SYNTH	C	38
Residential rehabilitation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV testing + informing of serostatus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV testing + informing of serostatus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
STI treatment	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medication for suicide prevention	-	-	-	-	?	-	A^{GEN}	40	-	-	-	-	-	-	-	-
Opioid prescribing limits	↓?	-	D^{GEN}	29	-	-	-	-	-	-	-	-	-	-	-	-
Abuse-deterrent opioid formulations	?	-	D^{GEN}	31	-	-	-	-	-	-	-	-	?	-	D	31
Prescription opioid monitoring programmes	?	-	D^{GEN}	32,41	-	-	-	-	-	-	-	-	?	-	D	41
Compulsory drug treatment/drug detention centres	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Criminalisation of drug use	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Notes on codes used in this table

Presence or absence of effect

✕ This intervention does not appear to have a significant effect upon the outcome
↑ This outcome may be increased by the intervention
↓This outcome is decreased by the intervention
- No evidence could be located of the impact of this intervention upon the outcome
? unclear evidence on impact of this intervention on the outcome

Level of evidence

A Consistent conclusions across meta-analyses, high quality systematic reviews, or multiple randomised controlled trials
B Evidence from one or two randomised controlled trials only
C High quality systematic reviews of cohort, case-control or cross-sectional studies
D Systematic reviews with inconsistent conclusions from authors or cross-sectional; OR multiple consistent ecological studies
E Cross-sectional association, case series suggesting outcome, single cohort study
GEN Evidence drawn from people who may not specifically use any drugs (including opioids)
PWID People who inject drugs that may not include opioids
ALC Note that this evidence pertains to people attending alcoholics anonymous
NE no pooled quantitative estimate reported

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Web appendix K: Details of literature search on cost-effectiveness studies to reduce overdose

We searched Medline for cost-effectiveness studies and other economic evaluations of opioid substitution therapy (methadone or buprenorphine, including new/emerging options such as implantable/depot formulations), naltrexone (oral or extended-release formulations), or naloxone, with overdose as the outcome of interest. Searches were completed 19 February 2018.

Search terms used were:

Group 1: Intervention		Group 2: Health economics	Results
"opioid substitution therapy" or OST or methadone or buprenorphine or "opioid agonist therapy" or "opioid replacement therapy"	+	"economic evaluation" or "cost effectiveness" or "cost benefit" or costs	176

Appendix L: Details of review on retention in treatment, dose of OST and other treatment characteristics

For data on retention in treatment, we used a recent modelling study by Mukandavire and colleagues[66] as well as an additional study supplied by one of the current paper's authors.[67] The Mukandavire study identified five observational population cohorts (with one presenting retention data separately by methadone and buprenorphine at cohort commencement) with at least five years of follow-up. Data from these studies were supplied and plotted.

We systematically reviewed published and grey literature to identify data on doses of methadone and buprenorphine prescribed in routine clinical practice, use of urine drug screening in treatment monitoring, and availability of unsupervised dosing in a country. Because the aim of the review was to describe OST as it is delivered in routine clinical practice, clinical guidelines were not consulted, and clinical trials and intervention studies were excluded. We included any cross-sectional or longitudinal observational study of people receiving OST with either methadone or buprenorphine. Studies were excluded if the sample was selected by demographic or clinical characteristics.

Search terms to identify peer-reviewed literature were as follows:

Pubmed

#	Terms	Results
1	(((((methadone[Title/Abstract]) OR methadone[MeSH Terms]) OR buprenorphine[Title/Abstract]) OR buprenorphine[MeSH Terms]) OR BMT[Title/Abstract]) OR MMT[Title/Abstract]	31505
2	(((((((("opioid substitution"[Title/Abstract]) OR "opiate substitution"[Title/Abstract]) OR "opioid replacement"[Title/Abstract]) OR "opiate replacement"[Title/Abstract]) OR "opioid agonist"[Title/Abstract]) OR "opiate agonist"[Title/Abstract]) OR opiate substitution treatment[MeSH Terms]) OR OST[Title/Abstract]) OR "opioid maintenance"[Title/Abstract]) OR "opioid maintenance"[Title/Abstract]	6942
3	Search 1 and search 2	2556
4	((((((((((("opioid substitution"[Title/Abstract]) OR "opiate substitution"[Title/Abstract]) OR "opioid replacement"[Title/Abstract]) OR "opiate replacement"[Title/Abstract]) OR "opioid agonist"[Title/Abstract]) OR "opiate agonist"[Title/Abstract]) OR opiate substitution treatment[MeSH Terms]) OR OST[Title/Abstract]) OR "opioid maintenance"[Title/Abstract]) OR "opioid maintenance"[Title/Abstract])) AND ((((((methadone[Title/Abstract]) OR methadone[MeSH Terms]) OR buprenorphine[Title/Abstract]) OR	811915

#	Terms	Results
	buprenorphine[MeSH Terms]) OR BMT[Title/Abstract]) OR MMT[Title/Abstract])	
5	Search 3 and search 4	399
6	((cohort[Title/Abstract]) OR longitudinal[Title/Abstract]) OR cross-sectional[Title/Abstract]	1913195
7	Search 3 and search 6	929
8	Search 3 and search 4 and search 6	157
9	Search 5 or search 7	1171
10	Search 9 restricted to post-2000	1067

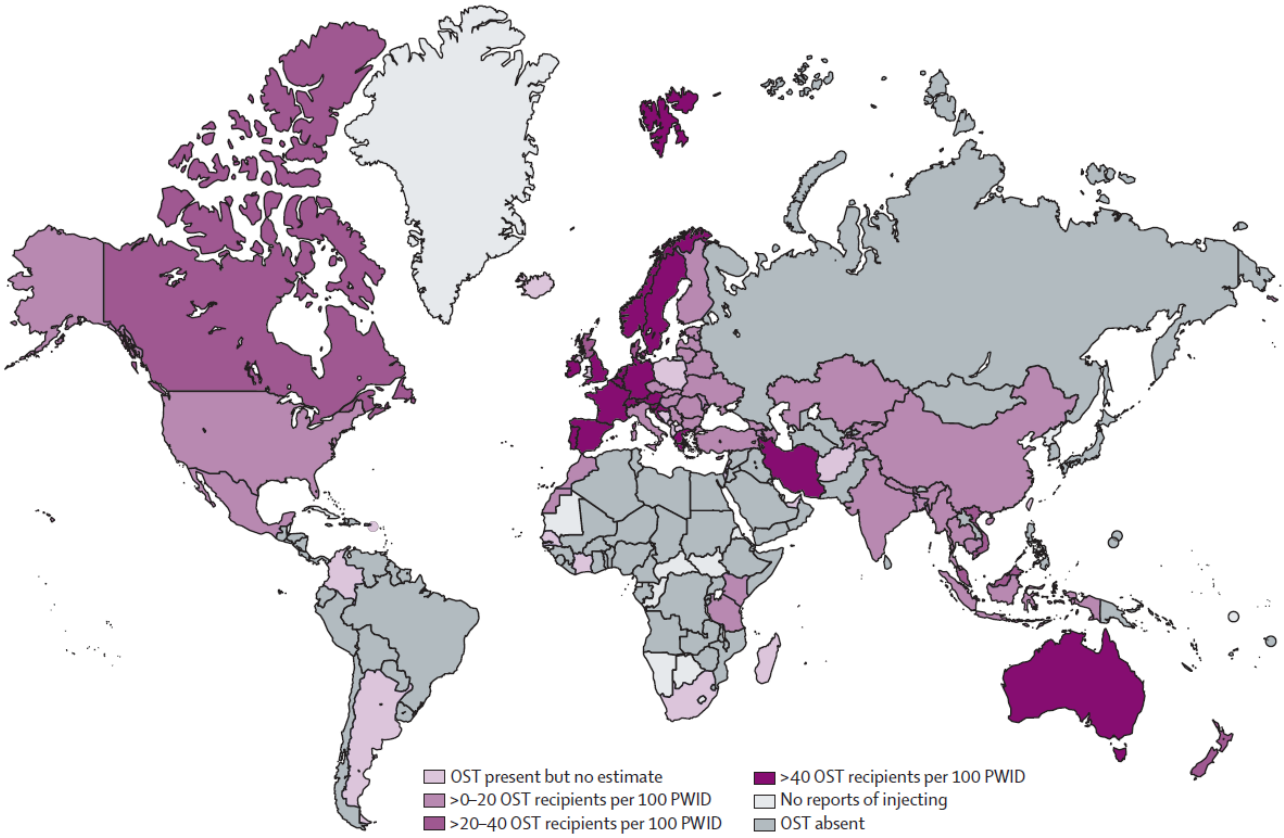
Embase

#	Terms	Results
1	methadone.ti,ab OR exp Methadone/ OR buprenorphine.ti,ab OR exp Buprenorphine/ OR BMT.ti,ab OR MMT.ti,ab	60181
2	("opioid substitution" OR "opiate substitution" OR "opioid replacement" OR "opiate replacement" OR "opioid agonist" OR "opiate agonist" OR "OST" OR "opioid maintenance" OR "opiate maintenance").ti,ab OR exp Opiate Substitution Therapy/	8240
3	Search 1 or search 2	65849
4	(methadone.ti,ab OR exp Methadone/ OR buprenorphine.ti,ab OR exp Buprenorphine/ OR BMT.ti,ab OR MMT.ti,ab) OR (("opioid substitution" OR "opiate substitution" OR "opioid replacement" OR "opiate replacement" OR "opioid agonist" OR "opiate agonist" OR "OST" OR "opioid maintenance" OR "opiate maintenance").ti,ab OR exp Opiate Substitution Therapy/)	1251739
5	Search 3 and search 4	4194
6	(cohort OR longitudinal OR cross-sectional).ti,ab	2284384
7	Search 3 and search 6	16303

#	Terms	Results
8	Search 3 and search 4 and search 6	894
9	Search 5 or search 7	19603
10	Search 9 restricted to post-2000	11900

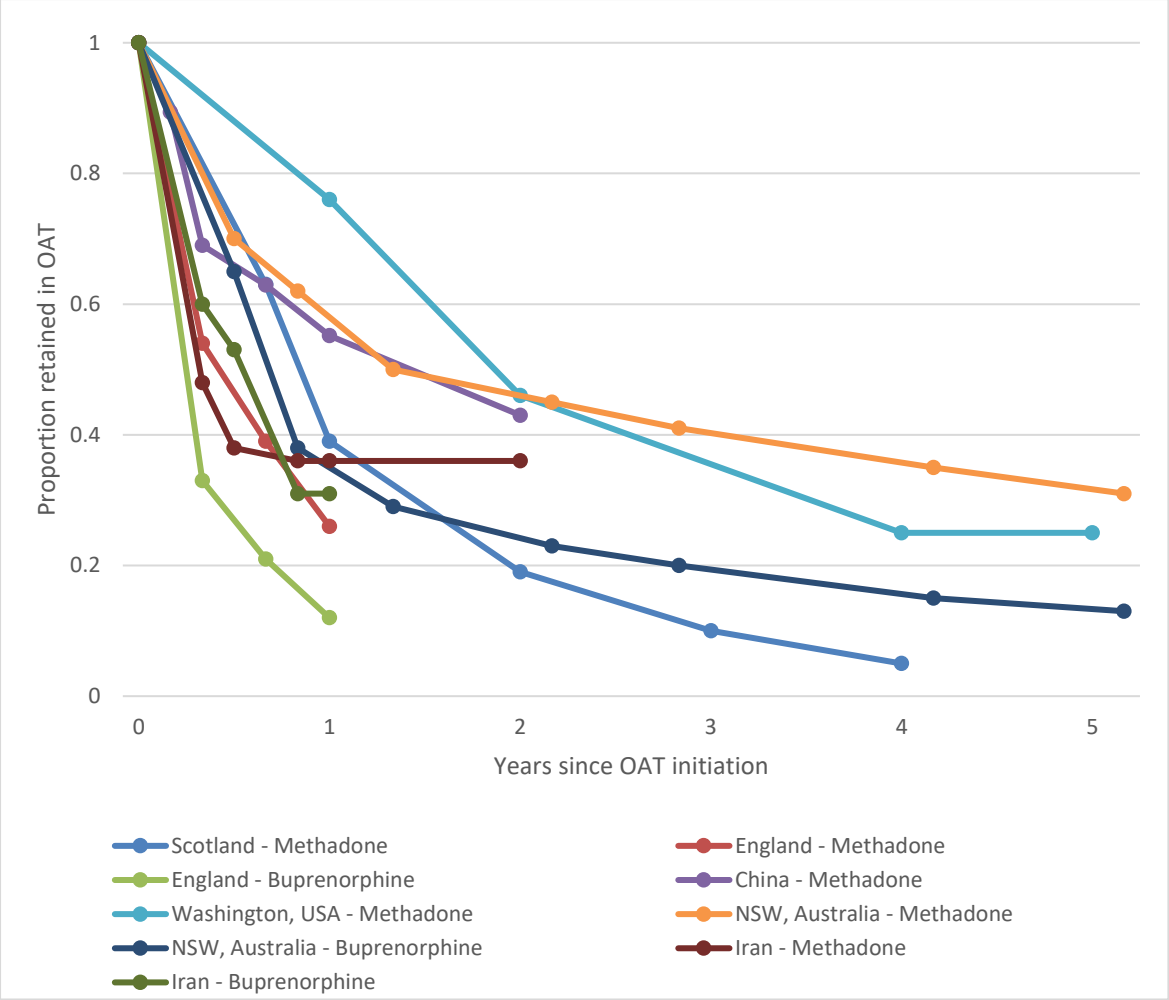
To identify data from the grey literature (i.e. reports and other material that is not formally published), we used a database collated for a systematic review of coverage of HIV prevention interventions for people who inject drugs.[68] This collection of 971 documents was assembled through extensive, systematic searching of websites related to HIV, hepatitis C virus, and/or injecting drug use. The database was searched for data on OST dose, urine drug screening, and availability of unsupervised dosing.

Figure L1: Number of people in opioid agonist treatment (OAT) per 100 people who inject drugs, 2015



Source: Figure reproduced from Larney al.[1]

Figure L2: Retention in OAT observed in large-scale cohorts



Note: Data extracted from Mukandavire et al.[2] and Hoseinie et al.[3].

References

1. Larney S, Peacock A, Leung J, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *The Lancet Global Health* 2017.

2. Mukandavire C, Low A, Mburu G, et al. Impact of opioid substitution therapy on the HIV prevention benefit of antiretroviral therapy for people who inject drugs. *Aids* 2017; **31**(8): 1181-90.

3. Hoseinie L, Gholami ZH, Shadloo B, Mokri A, Amin-Esmaeili M, Rahimi-Movaghar A. Drop-out from a drug treatment clinic and associated reasons. *Eastern Mediterranean Health Journal* 2017; **23**: 173-81.

Appendix M: Details of mathematical modelling

Model Description

A dynamic, deterministic, single-sex model of HIV and HCV transmission among current people who inject drugs (PWID) and people who used to inject drugs (ex-PWID) was developed. The model incorporates injecting transmission of HIV and HCV, sexual transmission of HIV among PWID, and tracks individuals following injecting cessation (ex-PWID) to fully capture HIV/HCV related mortality and life years lived. The model is stratified by injecting status (current PWID, ex-PWID), HCV disease status (susceptible, previously exposed, infected – F0, infected - F1, infected - infected - F2, infected - F3, infected - F4, infected - decompensated cirrhosis, infected - hepatocellular carcinoma), HIV disease status and stage (uninfected, acute infection, latent infection, AIDS, latent infection and on ART, AIDS and on ART), incarceration status (never incarcerated, currently incarcerated, released in the last 6 months, previously incarcerated but released longer than 6 months ago), and harm reduction status (off OAT, on OAT). Model schematics are shown in figure M1; model equations are at the end of this Appendix.

The model is open, such that individuals continually enter through initiation of injecting drug use as HCV and HIV uninfected PWID and off OAT. A proportion of PWID enter the model as never incarcerated and the remainder enter as previously incarcerated. PWID permanently cease injecting at a constant rate, whereby they leave the PWID compartment and enter the ex-PWID compartment. Individuals exit the model through mortality; PWID experience mortality through drug overdose, injury and suicide; both PWID and ex-PWID can experience HIV and HCV mortality and mortality through other causes (i.e. causes not related to suicide, drug overdose, HIV or HCV).

PWID enrol onto OAT at a time varying rate, which differs by incarceration state, and leave OAT at constant rates. A proportion of PWID entering or leaving OAT die due to the excess risk of overdose in the first 4 weeks after OAT initiation and discontinuation[69]. While on OAT, PWID have a reduced risk of mortality through all causes, with different reductions in risk during periods of incarceration compared to in the community (i.e. not incarcerated)[69-71]. While on OAT, PWID are assumed to have a reduced HIV and HCV transmission risk through injecting compared to those not on OAT[72,73]. PWID on OAT also have greater levels of viral

suppression whilst on ART, a greater rate of ART initiation and lower rate of loss to follow up than PWID not on OAT[74].

PWID are incarcerated or re-incarcerated at constant but different rates and are released from prison at a constant rate. The rate of incarceration or reincarceration is reduced if PWID are on OAT[75]. During incarceration, PWID have different overdose and suicide mortality rates compared to PWID in the community.[70] HIV and HCV transmission risk also differs in prison, and is higher in the 6 months following release than for never incarcerated PWID[76]. Depending upon OAT status at time of release[77,78], a proportion of PWID released from prison die due to the excess risk of overdose in the first 4 weeks following prison release[79].

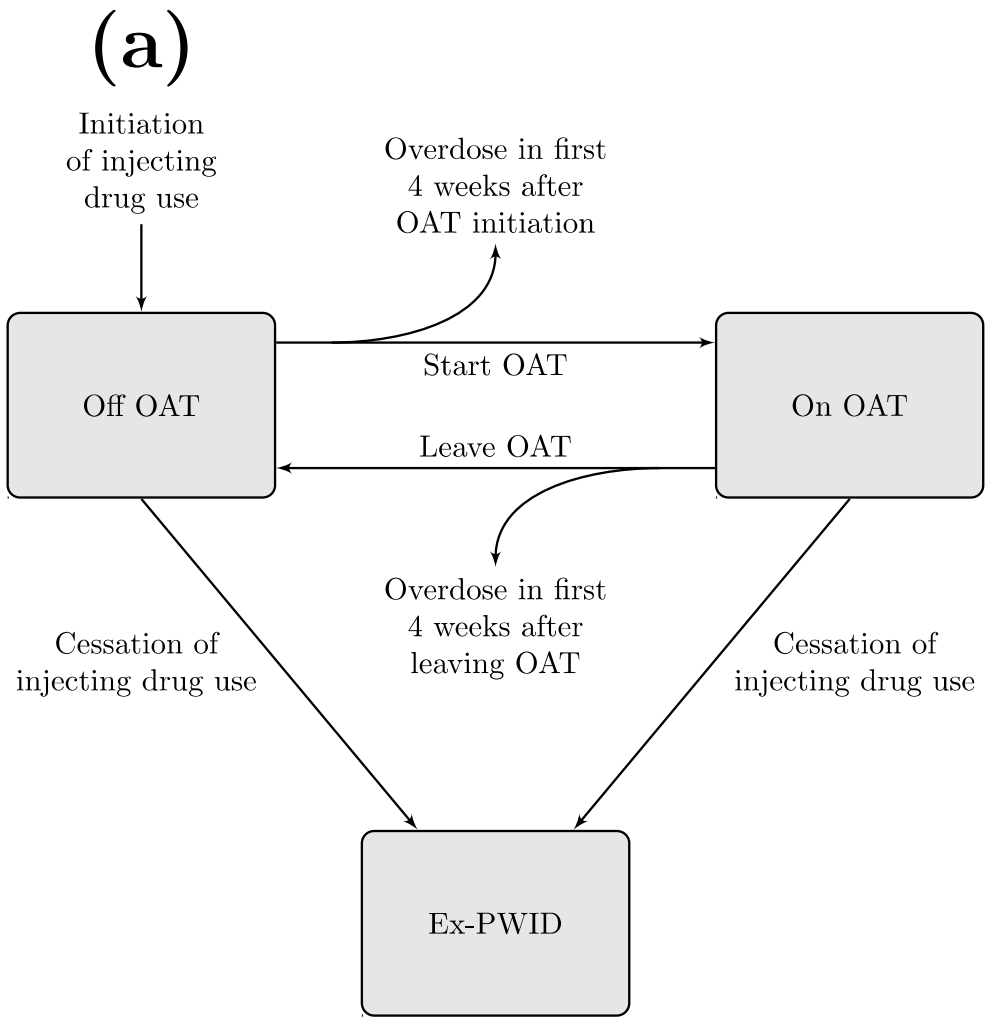
All PWID can acquire and transmit HCV through the sharing of injecting equipment in their given setting (prison or community). PWID susceptible to HCV become infected at a rate proportional to the chronic prevalence in their setting and the HCV transmission rate. PWID on OAT have lower HCV transmission risk, whilst recently released PWID have higher HCV transmission risk. The risk of HCV transmission may be higher or lower than in the community. PWID who are co-infected with HCV and HIV are assumed to be more likely to transmit HCV than those with HCV mono-infection. A proportion of those HCV infected (which depends upon HIV status) spontaneously clear their infection and remain in the susceptible compartment, the remainder enter the chronic HCV compartment.

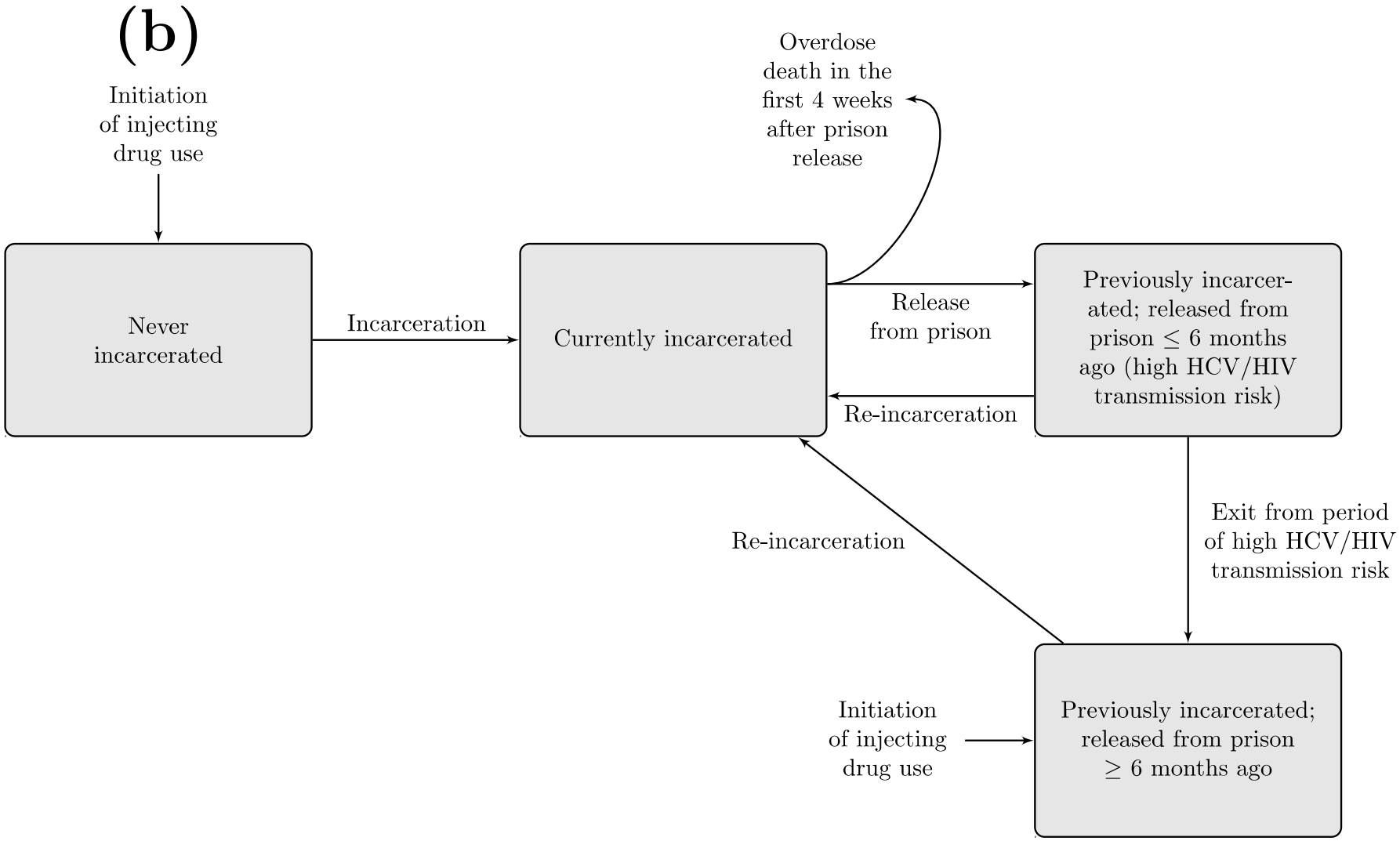
Individuals with chronic HCV infection advance from F0 through F1, F2, F3, to F4 (compensated cirrhosis) according to figure 1. Rates of progression from F0 to compensated cirrhosis are elevated if individuals are HIV infected, with these rates being lowered (compared to HIV infected individuals not on ART) if they are on ART[80]. Individuals with compensated cirrhosis develop decompensated cirrhosis and hepatocellular carcinoma (HCC), with individuals also developing HCC if they have decompensated cirrhosis. Individuals with decompensated cirrhosis or HCC leave the model through HCV-related mortality with the mortality rate for decompensated cirrhosis being elevated if HIV co-infected[81,82]. No HCV treatment is assumed in this modelling because treatment rates are currently very low in these settings.

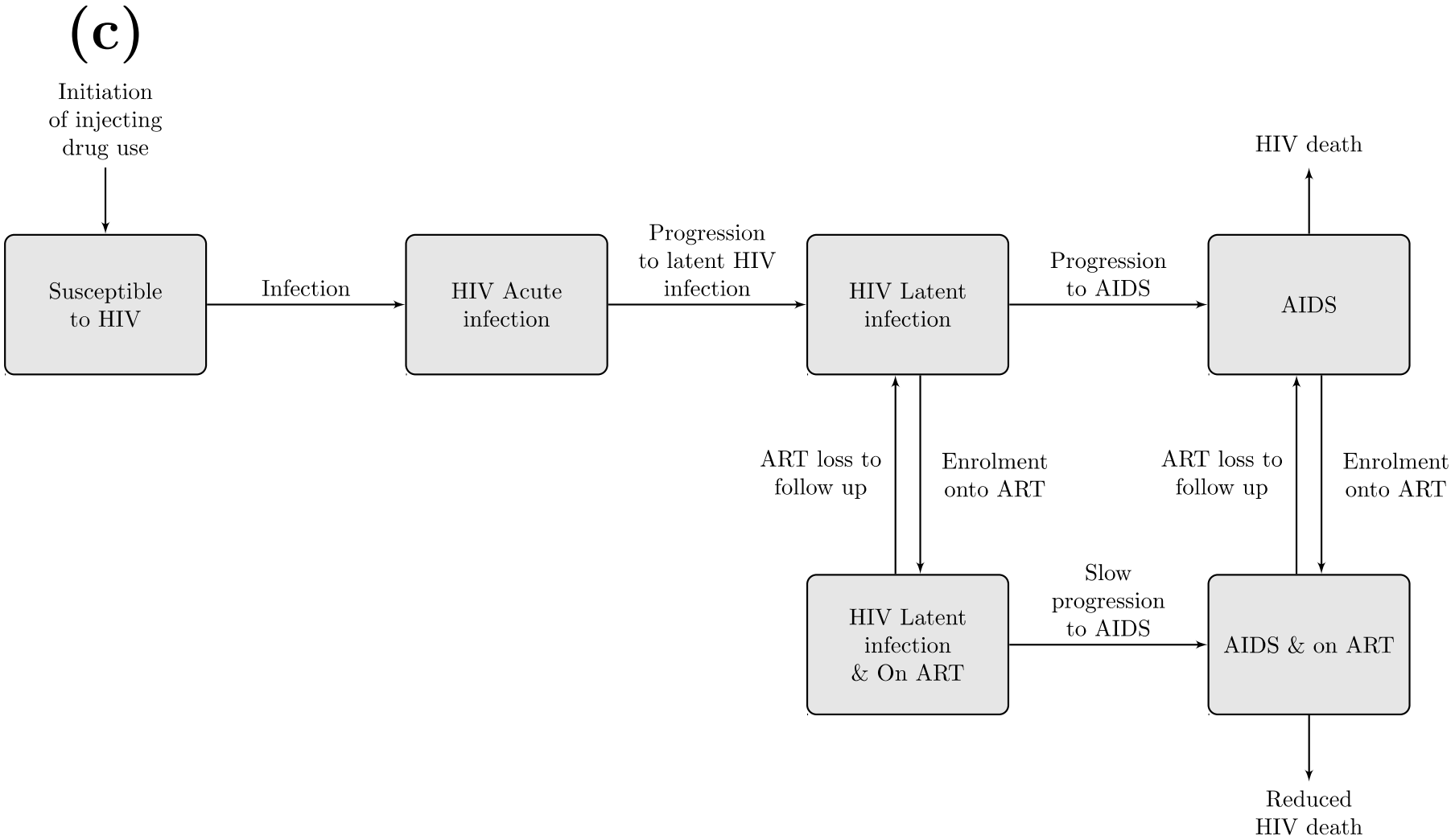
PWID susceptible to HIV are infected with a sexual and injecting force of infection which depends upon: the sexual and injecting HIV transmission rates, the proportions of PWID in

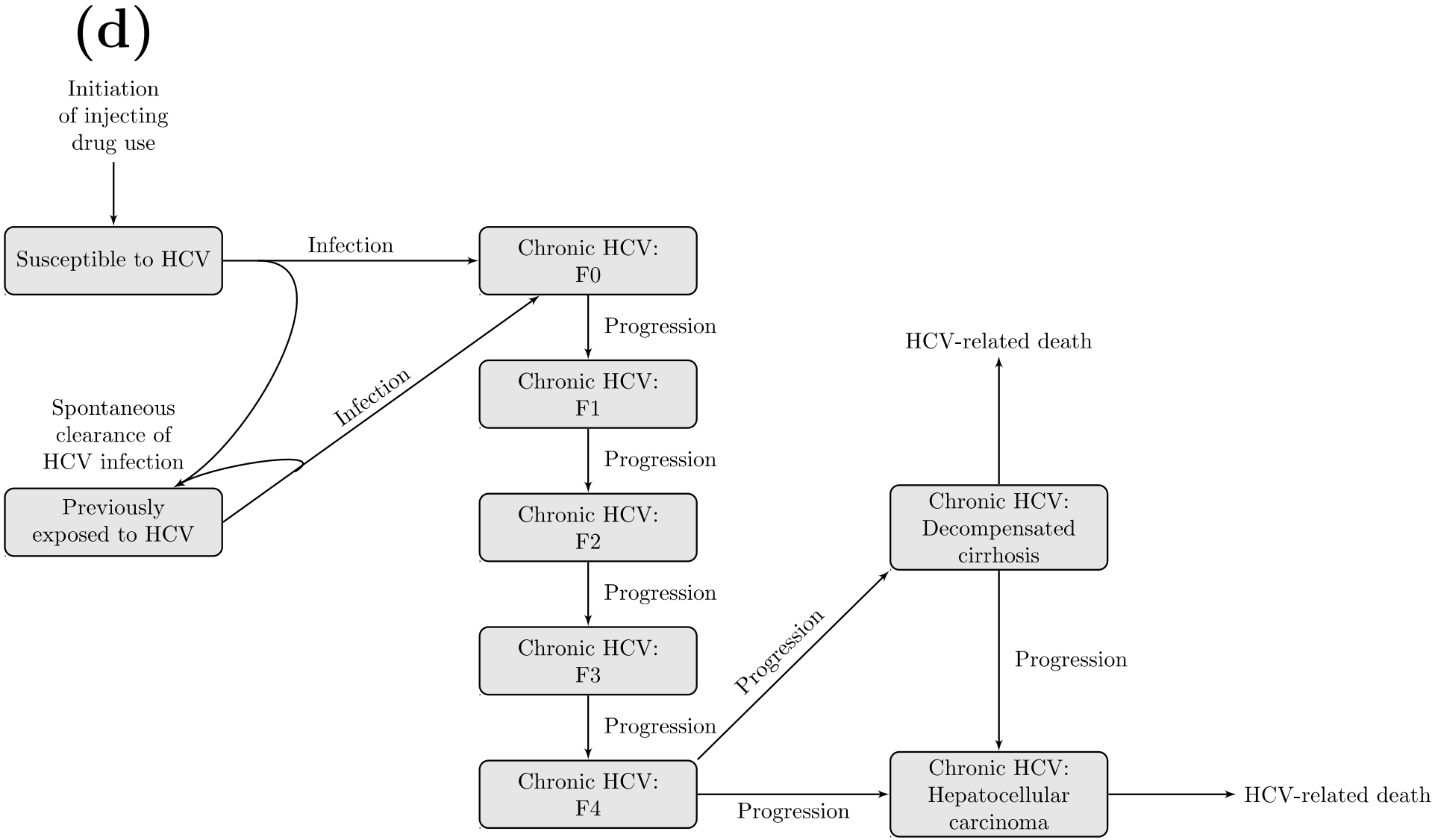
each stage of HIV infection in their setting (prison or the community), and the infectivity of each stage of infection (including ART status) which is measured relative to the latent phase of HIV infection. The model did not stratify PWID by sex and so sexual HIV transmission among PWID is modelled simply with no heterogeneity and all PWID in the community being able to mix freely to form sexual contacts. PWID on OAT have lower HIV transmission risk, whilst recently released PWID have higher HIV transmission risk through injecting. The risk of HIV transmission through injecting in prison may be higher or lower than in the community. We assume no sexual transmission whilst incarcerated due to the low levels of sex between men in prisons reported in the settings[83,84]. Following HIV infection, individuals enter a short acute phase of HIV infection, where they are assumed to be more infectious than in the subsequent latent phase of HIV infection[85] and progress from acute HIV infection to latent HIV infection at a fixed rate. Individuals progress from latent infection to AIDS at a constant rate, where it is assumed that individuals with AIDS who are not receiving ART do not engage in injecting drug use or sexual activity and so do not contribute to HIV transmission. Conversely, individuals with AIDS who are receiving ART are assumed to have the same HIV infectiousness as individuals with latent infection who are also receiving ART. Individuals with AIDS die from HIV related-disease at a constant rate and are removed from the model.Individuals with latent HIV infection and AIDS are enrolled onto ART at a constant rate. ART enrolment rates differ for current PWID and ex-PWID and are increased if PWID are on OAT[74]. Whilst on ART, individuals progress through the stages of HIV infection slower than individuals not on ART and experience a lower HIV mortality rate (when in the AIDS compartment only). The effectiveness of ART on reducing HIV infectiousness, progression and mortality depends on the proportion of individuals who are virally suppressed, which is higher amongst those receiving OAT[74]. Individuals receiving ART are lost to follow up at a constant rate which depends upon their injecting status, with PWID on OAT having better ART retention than PWID not receiving OAT[74]. The model assumes that these individuals can be re-enrolled onto ART at the same rate as ART-naïve individuals. ART retention and lost to follow-up are assumed to be the same in prison as the community. The proportion on ART who are virally supressed is assumed to be the same in prison and the community for those on and off OAT but differences in OAT coverage in prison and the community results in different levels of ART coverage and viral suppression in these settings.

Figure M1: Model schematics of (a) OAT component; (b) Incarceration component; (c) HIV transmission component; (d) HCV transmission and progression component.




(b)
Initiation of injecting drug use
Never incarcerated
Incarceration
Currently incarcerated
Overdose death in the first 4 weeks after prison release
Release from prison
Previously incarcerated; released from prison ≤ 6 months ago (high HCV/HIV transmission risk)
Re-incarceration
Re-incarceration
Exit from period of high HCV/HIV transmission risk
Initiation of injecting drug use
Previously incarcerated; released from prison ≥ 6 months ago


(c)
Initiation of injecting drug use
Susceptible to HIV
Infection
HIV Acute infection
Progression to latent HIV infection
HIV Latent infection
Progression to AIDS
AIDS
HIV death
ART loss to follow up
Enrolment onto ART
ART loss to follow up
Enrolment onto ART
HIV Latent infection & On ART
Slow progression to AIDS
AIDS & on ART
Reduced HIV death


(d)
Initiation of injecting drug use
Susceptible to HCV
Infection
Chronic HCV: F0
Progression
Chronic HCV: F1
Progression
Chronic HCV: F2
Progression
Chronic HCV: F3
Progression
Chronic HCV: F4
Spontaneous clearance of HCV infection
Previously exposed to HCV
Infection
Progression
Chronic HCV: Decompensated cirrhosis
HCV-related death
Progression
Chronic HCV: Hepatocellular carcinoma
Progression
HCV-related death

Model Parameterisation and Calibration

For Kiev, the model is primarily parameterised using data from three surveys; the 2015 and 2017 Alliance for Public Health Integrated Bio-Behavioural Assessment (IBBA) surveys[86,87] and the 2015 Expanding Medication-Assisted Therapy (ExMAT) bio-behavioural survey[88]. For Kentucky, the model is parameterised using data from the Social Networks Among Appalachian People study (denoted throughout as 'SNAP'), a longitudinal cohort of PWID whose methods have been described previously[89]. This included data on deaths and their causes for all PWID in the cohort. Based on this data, we model an increasing PWID population in Kentucky as done previously[90]. For Tehran, model parameterisation was informed by data from recent IBBAs as well as existing published data estimates, which were obtained from an exhaustive literature source of studies of PWID in these settings. Baseline and follow-up data from the standard of care arm of a recent Vanguard randomised controlled trial study[91] are used to parameterise mortality rates and causes of death in Kiev.

We calibrated the model using an approximate Bayesian computation sequential Monte Carlo scheme (ABC SMC)[92] to setting specific data on: HIV and HCV prevalence among PWID by incarceration status (community or currently incarcerated); the difference in HIV and HCV prevalence between previously incarcerated PWID and never incarcerated PWID; the difference in HCV prevalence between HIV positive PWID and HIV negative PWID; the proportion of PWID who have ever been incarcerated, or incarcerated twice or more; the proportion of PWID currently or ever on OAT or ART; all-cause mortality rates amongst PWID; the proportion of deaths among PWID that are HIV related or due to overdose, injury, suicide or other (not HIV-related, overdose, injury or suicide). During the ABC scheme, we estimate HCV and HIV transmission (injecting and sexual) rates, mortality rates of overdose, suicide, injury and other causes (excluding HIV and HCV), incarceration and re-incarceration rates and OAT and ART enrolment rates. The ABC scheme also estimates rates of HIV and HCV transmission through injecting whilst in prison based on differences in HIV and HCV prevalence among never incarcerated, currently incarcerated and previously incarcerated PWID and estimates levels of HIV sexual transmission among the community based on differences in HCV prevalence among HIV positive and HIV negative PWID.

The ABC SMC begins with 500 parameter sets sampled from prior distributions, using Latin Hypercube sampling, which are then resampled and perturbed in an iterative manner so that each time the parameter sets better fit the data, until successive iterations no longer significantly improve the goodness of the fits as defined by a 'distance function'.

For Kentucky, this distance function is given by the log likelihood of the data given the parameters with the following contributing to the likelihood:

- HCV prevalence among never incarcerated PWID (using a beta pdf)
- HCV prevalence among previously incarcerated PWID (using a beta pdf)
- The proportion of community PWID who have ever been incarcerated (using a beta pdf)

- The proportion of community PWID who have been incarcerated twice or more (using a beta pdf)
- The proportion of PWID currently on OAT (using a beta pdf)
- The mortality rate among PWID (using a gamma pdf)
- The proportion of deaths due to each cause (using a dirichlet pdf)

For Kyiv, this distance function is given by the log likelihood of the data given the parameters with the following contributing to the likelihood:

- HCV prevalence among community PWID (using a beta pdf)
- HIV prevalence among community PWID (using a beta pdf)
- The odds ratio of the HCV prevalence among community PWID who have ever been incarcerated compared to those who have never been incarcerated (using a lognormal pdf)
- The odds ratio of the HIV prevalence among community PWID who have ever been incarcerated compared to those who have never been incarcerated (using a lognormal pdf)
- The odds ratio of the HCV prevalence among HIV positive PWID in the community compared to HIV negative PWID in the community (using a lognormal pdf)
- The proportion of community PWID who have ever been incarcerated (using a beta pdf)
- The proportion of community PWID who have been incarcerated twice or more (using a beta pdf)
- The proportion of PWID currently on OAT (using a beta pdf)
- The proportion of PWID ever on OAT (using a beta pdf)
- The mortality rate among PWID (using a gamma pdf)
- The proportion of deaths due to each cause (using a dirichlet pdf)

For Tehran, this distance function outputs a vector of two elements [a,b], with both elements of the vector being improved between iterations of the ABC algorithm. This was done to allow for additional uncertainty such that OAT and ART coverages among PWID must only fall within a range which are based on either national data or estimates from other cities in Iran. The first element (a) is a measure of how far the model projections for OAT coverage among all PWID, OAT coverage among incarcerated PWID and ART coverage among HIV positive PWID are from the corresponding ranges that are informed by data. Specifically,

$$a = \sum_{i=1,2,3} f(x_i, y_i, z_i)$$

Where

- x_1, x_2 and x_3 are the model projections for OAT coverage among all PWID, OAT coverage among incarcerated PWID and the ART coverage among HIV positive PWID, respectively.
- y_1, y_2 and y_3 are the lower limits of the target calibration range for OAT coverage among all PWID, OAT coverage among incarcerated PWID and the ART coverage among HIV positive PWID, respectively.

- z_1, z_2 and z_3 are the upper limits of the target calibration range for OAT coverage among all PWID, OAT coverage among incarcerated PWID and the ART coverage among HIV positive PWID, respectively.
- $f(x,y,z) = \begin{cases} \frac{\left(x-\frac{y+z}{2}\right)^2}{\frac{y+z}{2}} & if\ x < y\ or\ x > z \\ 0 & if\ y \leq x \leq z \end{cases}$

The second element (b) is the log likelihood of the data given the parameters with the following contributing to the likelihood:

- HCV prevalence among community PWID (using a beta pdf)
- HIV prevalence among community PWID (using a beta pdf)
- HCV prevalence among currently incarcerated PWID (using a beta pdf)
- HIV prevalence among currently incarcerated PWID (using a beta pdf)
- The odds ratio of the HCV prevalence among community PWID who have ever been incarcerated compared to those who have never been incarcerated (using a lognormal pdf)
- The odds ratio of the HIV prevalence among community PWID who have ever been incarcerated compared to those who have never been incarcerated (using a lognormal pdf)
- The odds ratio of the HCV prevalence among HIV positive PWID in the community compared to HIV negative PWID in the community (using a lognormal pdf)
- The proportion of community PWID who have ever been incarcerated (using a beta pdf)
- The proportion of community PWID who have been incarcerated twice or more (using a beta pdf)
- The proportion of PWID currently on OAT (using a beta pdf)
- The proportion of PWID ever on OAT (using a beta pdf)
- The mortality rate among PWID (using a gamma pdf)
- The proportion of deaths due to each cause (using a dirichlet pdf)

Table M1 summarises the parameter values used that do not vary by setting. The increases in the risk of overdose mortality in the first 4 weeks in and out of OAT and the effects of OAT on overdose mortality in the community, HIV and HCV transmission and HIV treatment outcomes are based on pooled effect estimates from systematic reviews of international evidence. Other effects of OAT, including the effect on mortality from suicide, injury and other causes (excluding overdoses, HIV and HVC) in the community, the effect on mortality from unnatural causes (injury, suicide and overdose) in prisons and the effect on incarceration rates, are parametrised using estimates from single studies. Tables of setting specific parameter values and calibration targets are in Tables M2-M7. Model fits to data on HIV and HCV prevalence data and rates of mortality are shown in Figures M2-M9.

A simplified model without ex-PWID and HCV disease progression is used for model calibration, assuming that HCV deaths will not occur in the time frame of PWID's duration of injecting. After model calibration, for each model run we sample parameters related to HCV

disease progression and mortality, the proportion of PWID that are male and the average age that PWID start injecting from setting-specific parameter ranges to calculate mortality rates among ex-PWID, using national life expectancy data[93].

Table M1: Parameter distributions that do not vary by setting.

Parameter	Symbol	Parameter Value	Source/ Notes
Effects of OAT: Mortality			
Relative risk of overdose mortality if on OAT outside of prison	OAT_o^c	0.25 (95%CI: 0.18-0.36)	[69] Lognormal distribution
Relative risk of suicide mortality if on OAT outside of prison	OAT_s^c	0.48 (95%CI: 0.39-0.59)	[71] Lognormal distribution
Relative risk of injury mortality if on OAT outside of prison	OAT_l^c	0.40 (95%CI: 0.34-0.46)	[71] Lognormal distribution
Relative risk of other causes of mortality if on OAT	OAT_a	0.86 (95%CI:0.75-0.99)	[71] Lognormal distribution
Relative risk of suicide, injury and overdose mortality if on OAT in prison	OAT_s^p, OAT_l^p, OAT_o^p	0.13 (95%CI: 0.05-0.35)	[70] Lognormal distribution
Relative risk of overdose in first 4 weeks after prison release if on OAT at time of release (independent of whether retained on release).	OAT_o^{rel}	0.25 (95%CI: 0.14-0.45)	[71] Lognormal distribution
Relative risk of overdose in first 4 weeks of OAT vs rest of time on OAT	OAT_{start}	1.85 (95%CI: 0.93-3.66)	[69,94] Lognormal distribution
Relative risk of overdose in first 4 weeks off OAT vs rest of time on OAT	OAT_{leave}	1.98 (95%CI: 1.24-3.15)	[69,94] Lognormal distribution
Effects of OAT: HIV/HCV transmission			
Relative risk of HIV IDU transmission if on OAT	OAT_{HIV}	0.46 (95%CI: 0.32-0.67)	[72] Lognormal distribution
Relative risk of HCV IDU transmission if on OAT	OAT_{HCV}	0.50 (95%CI: 0.40-0.63)	[73] Lognormal distribution
Effects of OAT: HIV treatment			
Relative risk of ART recruitment if on OAT	$\frac{\Omega_1}{\Omega_0}$	1.87 (95%CI: 1.50-2.33)	[74] Lognormal distribution
Relative risk of ART LTFU if on OAT	$\frac{\Gamma_1}{\Gamma_0}$	0.77 (95%CI: 0.63-0.95)	[74] Lognormal distribution
Increase in odds of viral suppression if on OAT vs off OAT	$\frac{p_s^*(1-p_s)}{p_s(1-p_s^*)}$	1.45 (95%CI: 1.21-1.73)	[74] Lognormal distribution
Effects of OAT: Incarceration			
Relative rate of re/incarceration if on OAT	OAT_{inc}	0.79 (95%CI: 0.70–0.89)	[75] Lognormal distribution.
HIV Disease Progression			
Average length of HIV acute stage in months	$\frac{12}{\delta_a}$	2.90 (95%CI: 1.23-6.0)	[85] Triangular distribution.
Time from seroconversion to AIDs in years	$\frac{1}{\delta_l}+\frac{1}{\delta_a}$	Median 9.4 (IQR: 5.5-10.1)	[95] Triangular distribution.
Median time to death from AIDS in months	$\frac{12}{\mu_{HIV}}$	9.2 (IQR: 2.2-23.6)	[95] Triangular distribution.
HIV transmissibility in acute stage of infection (ω_1)	$\omega_a = \frac{\omega_1}{\omega_2}$	276 (95%CI: 131-509)	[85] Lognormal distribution

HIV transmissibility in latent stage of infection (ω_2)	$\omega_a = \frac{\omega_1}{\omega_2}$	10.6 (95%CI: 7.61-13.3)	[85] Lognormal distribution
ART Parameters			
Reduction in HIV progression if on ART and virally suppressed	t_p	0.1-0.44	[96] Lognormal distribution.
Increase in HIV progression in non-virally supressed on ART vs virally supressed (VL<500)	t_s	3.07 (2.43-3.89)	[97] Lognormal distribution. N.B. In the model, the reduction in HIV progression among those on ART who are not virally supressed is capped at 1. [66,97,98]
Average log viral Load if not on ART	v_b	4.79 (IQR: 4.11-5.27)	Triangular distribution – International data [66,97,98]
Average reduction in log viral Load if on ART and not virally supressed	Δ_u	0.81 IQR (0-2.27)	Triangular distribution – International data
Factor difference in HIV transmission risk for each log increment PVL	r_t	2.45 (95%CI: 1.85-3.26)	[99] Lognormal distribution – International data
HIV/HCV Transmission			
Relative increase in HCV transmission rate compared to HIV transmission rate through injecting	$\frac{\lambda}{\zeta}$	4.0-10.0	[100] Uniform distribution
Increase in HCV infectiousness if HIV positive	η_2	1.0-7.0	[100] Uniform distribution
Increase in HIV/HCV injecting transmission risk if currently incarcerated or recently released from prison compared to other PWID in the community	η_1	1.72 (range: 1.28 – 2.34)	[76] Triangular distribution: mode is average of HCV and HIV effects and range and lower/upper bounds to be the minimum/ maximum of 95%CI intervals for these estimates.

			N.B. different rate used for Kentucky (See Table M4)
Mortality			
Relative risk of overdose mortality in first 1-2 weeks after prison release vs 5-12 weeks in community (R_{r1})	$R_r = \frac{R_{r1} + R_{r2}}{2}$	Range: 3.2-10.0	[79] Uniform distribution. Take average of effect w1-2 and w3-4
Relative risk of overdose mortality in first 3-4 weeks after prison release vs 5-12 weeks in community (R_{r2})	$R_r = \frac{R_{r1} + R_{r2}}{2}$	1.7 (95%CI: 1.3-2.2)	[79] Lognormal distribution. Take average of effect w1-2 and w3-4
Relative risk of overdose mortality during prison vs community	R_o	0.03-0.17	[70,71] Uniform distribution
Relative risk of injury mortality during prison vs community	R_i	0.03-0.3	[70,71] Uniform distribution
Relative risk of mortality through other causes (not suicide, overdose, injury, HIV or HCV-related death) during prison vs community	R_a	0.07-0.28	[70,71] Uniform distribution
HCV Disease progression			
% infections that spontaneous clear if HIV negative	α_-	26% (95%CI: 22.0-29.0)	[101] Normal Distribution.
% decrease in odds of spontaneous clearance if HIV positive	$\frac{\alpha_+(1-\alpha_-)}{\alpha_-(1-\alpha_+)}$	0.58 (95% CI: 0.38-0.88)	[102] Lognormal Distribution.
Annual rate of progression from F0 to F1 in HIV negative*	$\sigma_{3,4}^0$	0.128 (95%CI: 0.08-0.176)	[103] Normal distribution
Annual rate of progression from F1 to F2 in HIV negative*	$\sigma_{4,5}^0$	0.059 (95%CI: 0.035-0.082)	[103] Normal distribution
Annual rate of progression from F2 to F3 in HIV negative*	$\sigma_{5,6}^0$	0.079 (95%CI: 0.056-0.10)	[103] Normal distribution
Annual rate of progression from F3 to F4 in HIV negative*	$\sigma_{6,7}^0$	0.116 (95%CI: 0.07-0.161)	[103] Normal distribution
Relative risk of progression to cirrhosis if on ART vs HIV positive not on ART*	$\frac{\sigma_{3,4}^4}{\sigma_{3,4}^3}$	0.27-0.70	[80,104] Uniform distribution
Relative risk of progression to cirrhosis if HIV positive*	$\frac{\sigma_{3,4}^3}{\sigma_{3,4}^0}$	2.489 (95%CI: 1.811-3.42)	[80] Lognormal distribution
Annual probability of progression to decompensated cirrhosis from F4*	$1 - e^{-\sigma_{7,8}^0}$	0.039	[105] Beta(14.6168,360.1732)
Annual probability of death from decompensated cirrhosis if HIV negative*	$1 - e^{-\mu_{DC}^0}$	0.13	[105] Beta(147.03,983.97)

Relative risk of mortality from decompensated cirrhosis if HIV positive vs negative*	$\frac{\mu_{DC}^{3}}{\mu_{DC}^{0}}$	2.26 (95%CI: 1.51-3.38)	[81,82] Lognormal distribution
Annual probability of progression to HCC from F4 or decompensated cirrhosis*	$1-e^{-\sigma_{7,9}^{0}}$	0.014	[105] Beta(1.9326,136.1732)
Annual probability of death from HCC*	$1-e^{-\mu_{HCC}}$	0.43	[105] Beta(117.1033, 155.23)

* Parameter sampled after ABC SMC routine.

Table M2: Prior parameter distributions specific to Kentucky

Parameter	Symbol	Prior	Estimates	Source
Proportion PWID who are male		Uniform (53.6-63.5)	58.6% (53.6-63.5)	SNAP cohort[83]
Duration of injecting (years)	$\frac{1}{v}$	Uniform (5-25 years)	Mean: 10.5 (95%CI: 9.7-11.2)	SNAP cohort[83]
Age at first injection		Uniform: (17-26)	Median: 20.5 (IQR: 17-26)	SNAP cohort[83]
% of PWID who start injecting prior to first incarceration	$\frac{\phi_{0,0}^{1,0}}{\phi_{0,0}^{4,0}}$	Uniform (43.5-62.7%)	48.5% (95%CI: 43.5-53.4) have age at first injection < age at first incarceration. 57.9% (95%CI: 52.9-62.7) have age at first injection <= age at first incarceration	SNAP cohort[83]
Average length of one incarceration (months)	$\frac{12}{\tau}$	Normal with mean 3.40 and 95%CI: 2.70-4.09	3.40 (95% CI: 2.70 – 4.09).	SNAP cohort[83]
Increased risk if currently or recently incarcerated	η_1	Lognormal with mean 2.80 and 95%CI: 1.36-5.77	2.80 (95%CI: 1.36-5.77)	SNAP cohort[83]
OAT start date		Uniform: (1990-1999)	1990-1999	

Table M3: Data for model calibration in Kentucky

Parameter	Estimates	Source/Notes
	HCV antibody prevalence	
HCV Prevalence among never incarcerated PWID	43.4% (95%CI: 38.1-48.8)	SNAP cohort[83]
HCV Prevalence among previously incarcerated PWID	56.6% (95%CI: 51.2-61.9)	SNAP cohort[83]
	Incarceration data	
Proportion ever incarcerated	84.7% (95%CI: 80.8-87.9)	SNAP cohort[83]
Proportion incarcerated twice or more	71.2% (95%CI: 66.5-75.5%)	SNAP cohort[83]
	OAT Coverage	
Proportion of PWID currently on OAT	4.7% (95% CI: 3.8-5.8%) in 2009.	SNAP cohort[83]
OAT LTFU rate.	132-352/100pyrs	SNAP cohort[83]
	Mortality	
Overall mortality rate	0.95/100py (0.64-1.42)	SNAP cohort[83]
% of deaths that are		SNAP cohort[83]. 27/35 observed deaths had recorded causes. 7 deaths were overdose, 2 deaths were suicides, 2 deaths were injuries, 16 deaths were other medical causes.
Overdose	25.9% (95%CI: 11.1-46.3)	
Suicide	7.4% (95%CI: 0.9-24.3)	
Injury	7.4% (95%CI: 0.9-24.3)	
Other	59.3% (95%CI: 38.8-77.6)	

Figure M2: A comparison of model fits for Kentucky with HCV prevalence estimates among (a) PWID in the community, and (b) incarcerated PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HCV prevalence data points with 95% confidence intervals.

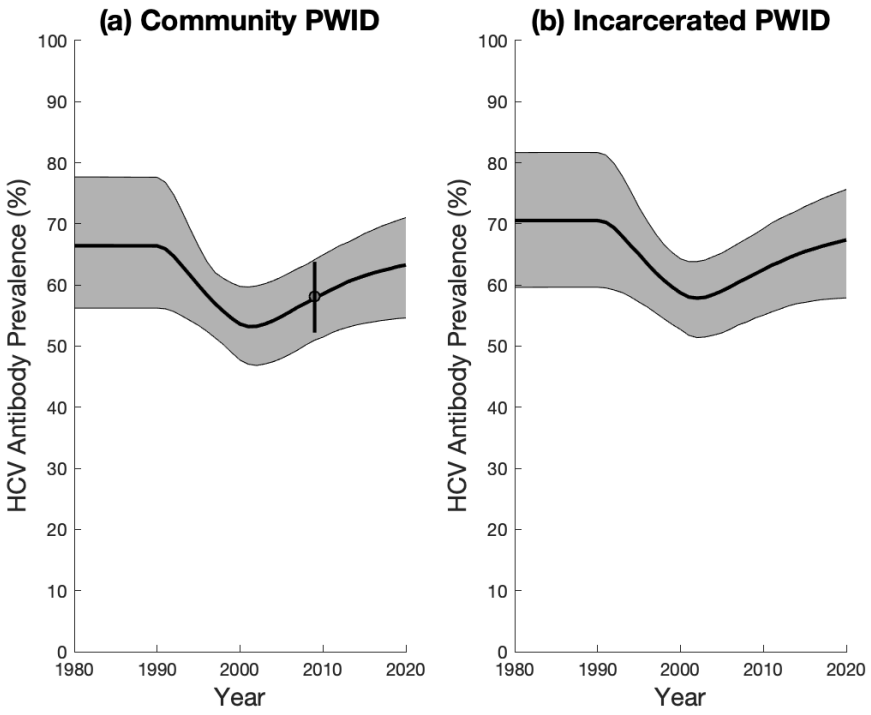


Figure M3: A comparison of model fits for Kentucky with mortality estimates among current PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HIV prevalence data points with 95% confidence intervals.

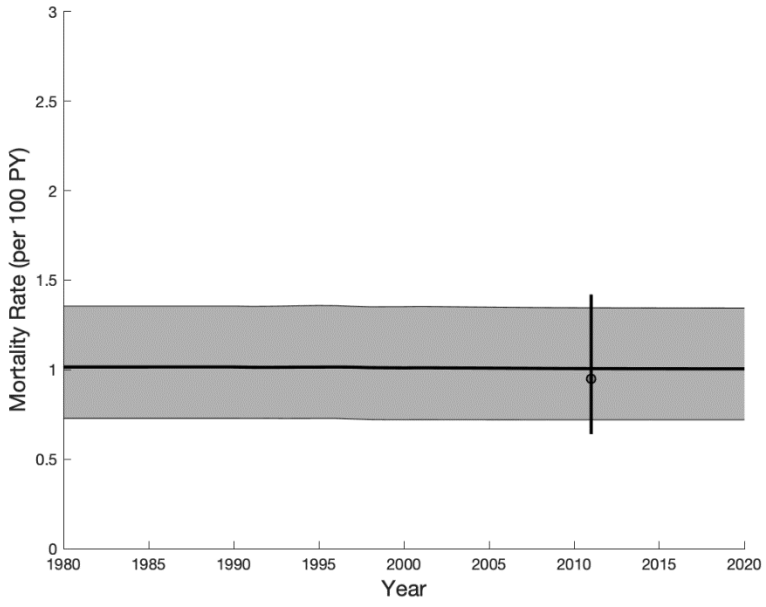


Table M4: Prior parameter distributions specific to Kiev

Parameter	Symbol	Prior	Estimates	Source
Proportion PWID who are male		Uniform (69.9-93.1%)	74.3% (95%CI: 69.9-88.3)	ExMAT 2014[82]
			90.0% (95%CI: 86.4-93.1)	IBBA 2015[80]
			80.5% (95%CI: 74.6-85.9)	IBBA 2017[81]
Duration of injecting (years)	$\frac{1}{v}$	Uniform (6.5-30)	Median: 13 (IQR: 9-17)	ExMAT 2014[82]
			Median: 14 (IQR: 8-18)	IBBA 2015[80]
		0.5* lowest estimate to 2* highest estimate	Median 15 (IQR: 8-21)	IBBA 2017[81]
Age at first injection		Uniform (16-23)	Median: 18 (IQR:16-20)	ExMAT 2014[82]
			Median: 19 (IQR: 17-23)	IBBA 2015[80]
			Median: 19 (IQR: 16-23)	IBBA 2017[81]
% of PWID who start injecting prior to first incarceration	$\frac{\phi_{0,0}^{1,0}}{\phi_{0,0}^{4,0}}$	Uniform (89.8-98.4%)	92.7% (95%CI: 89.8-94.9) have age of first injection < age of first incarceration	ExMAT 2014[82]
			2.9% (1.6-5.1%) have age of first injection > age of first incarceration	
Average length of one incarceration (months)	$\frac{12}{\tau}$	Uniform (10.0-13.0)	Range: 10.0-13.0	ExMAT 2014[82]. Range from Monte Carlo simulations to account for time spent in pre-trial detention (sizos) and prisons.
ART LTFU (per 100 py)	Γ_0	Uniform (10.6 – 16.2)	LTFU among non-PWID: 9.98 per 100 py (95%CI: 9.64-11.32); RR PWID vs non-PWID: 1.26 (95%CI: 1.10-1.43)	[100] Eastern Europe
% Of PWID on ART virally suppressed	p_s	Lognormal with mean 68.3% and 95%CI: 46.9-84.0)	68.3% (95%CI: 46.9-84.0)	IBBA 2017[81] Assumed not to vary over time.

Table M5: Data for model calibration in Kiev

Parameter	Estimates	Source/Notes
HIV Prevalence		
HIV prevalence among community PWID	26.6% (95%CI: 20.3-33.3)	ExMAT 2014[82]
	21.7% (95%CI: 15.7-28.2)	IBBA 2015[80]
	25.6% (95%CI: 19.7-31.8)	IBBA 2017[81]
Odds ratio: ever incarcerated vs never incarcerated PWID	2.74 (95%CI: 1.78-4.20)	ExMAT 2014[82]
	1.52 (95%CI: 0.91-2.54)	IBBA 2015[80]
	1.98 (95%CI: 1.22-3.23)	IBBA 2017[81]
HCV antibody prevalence		
HCV prevalence among community PWID	84.8% (95%CI: 78.5-90.1)	ExMAT 2014[82]
	64.4% (95%CI: 59.6-69.0)	IBBA 2015[80]
	77.3% (95%CI: 71.1-83.1)	IBBA 2017[81]
Odds ratio: ever incarcerated vs never incarcerated PWID	1.38 (95%CI: 0.77-2.46)	ExMAT 2014[82]
	1.57 (95%CI: 1.00-2.48)	IBBA 2015[80]
	2.70 (95%CI: 1.56-4.67)	IBBA 2017[81]
Odds ratio: HIV positive PWID vs HIV negative PWID	1.04 (95%CI: 0.56-1.93)	ExMAT 2014[82]
	2.32 (95%CI: 1.29-4.15)	IBBA 2015[80]
	1.32 (95%CI: 0.73-2.40)	IBBA 2017[81]
Incarceration data		
% Ever incarcerated	49.0% (95%CI: 43.0-55.1)	ExMAT 2014[82]
% Incarcerated twice or more	32.1% (95%CI: 27.6-36.9)	ExMAT 2014[82]
OAT Coverage		
Proportion of PWID ever on OAT	7.8% (95%CI: 4.9-10.9)	IBBA 2013
	15.7% (95%CI: 11.0-20.9)	IBBA 2015[80]
	21.2% (95%CI: 16.0-26.8)	IBBA 2017[81]
Proportion of PWID currently on OAT	4.4% (95%CI: 2.2-7.2)	IBBA 2015[80]
	4.5% (95%CI: 2.0-7.6)	IBBA 2017[81]
ART Coverage		
Proportion of HIV+ve that self-report ART	20.9% (95%CI: 12.7-32.5)	ExMAT 2014[82]
	25.8 (95%CI: 16.6-37.0)	IBBA 2017[81]
Mortality		
Overall mortality rate (per 100 py) among PWID	5.6 (95%CI: 3.7 – 8.3)	Vanguard [85] HIV positive PWID contribute 184.7py and HIV negative PWID contribute 275.7py. Model mortality rate is weighted to account for this during calibration.
% of deaths that are		Vanguard [85]. 16/25 observed deaths had recorded causes. 3 deaths were HIV related, 3 deaths were overdose, 10 deaths were other medical causes. 6 deaths among HIV positive PWID were from unknown causes (2 with CD4 counts<200). Of the unclassified deaths, we assume there were 0.5 suicide deaths, 0.5 injury deaths, 2 HIV deaths and 6 deaths from other causes.
HIV related	20% (95%CI: 6.83-40.7)	
Overdose	12% (95%CI: 2.6-31.2)	
Suicide	2.0% (95%CI: 0.0-17.2)	
Injury	2.0% (95%CI: 0.0-17.2)	
Other	64.0% (95%CI: 42.5-82.0)	

Figure M4: A comparison of model fits for Kiev with HIV prevalence estimates among (a) PWID in the community, and (b) incarcerated PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HIV prevalence data points with 95% confidence intervals.

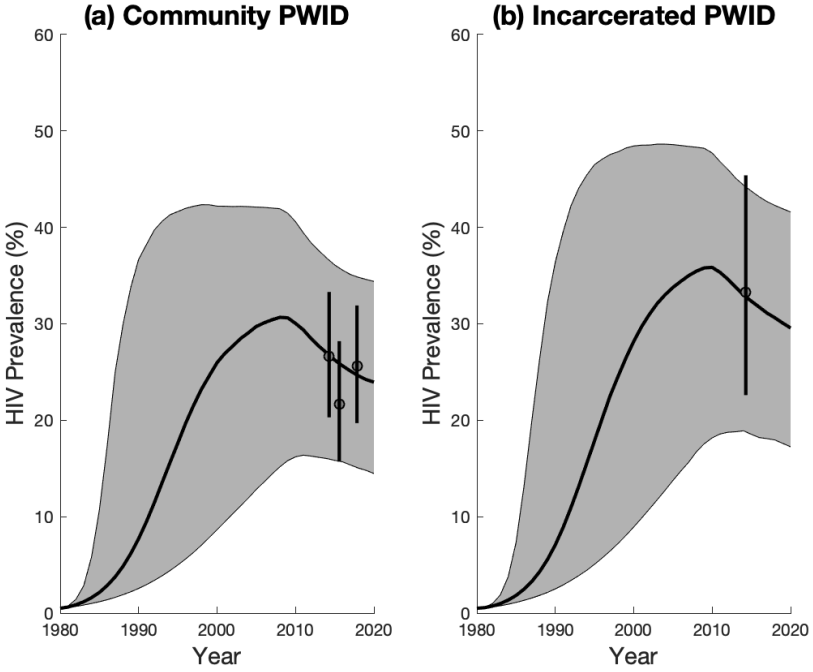


Figure M5: A comparison of model fits for Kiev with HCV prevalence estimates among (a) PWID in the community, and (b) incarcerated PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HCV prevalence data points with 95% confidence intervals.

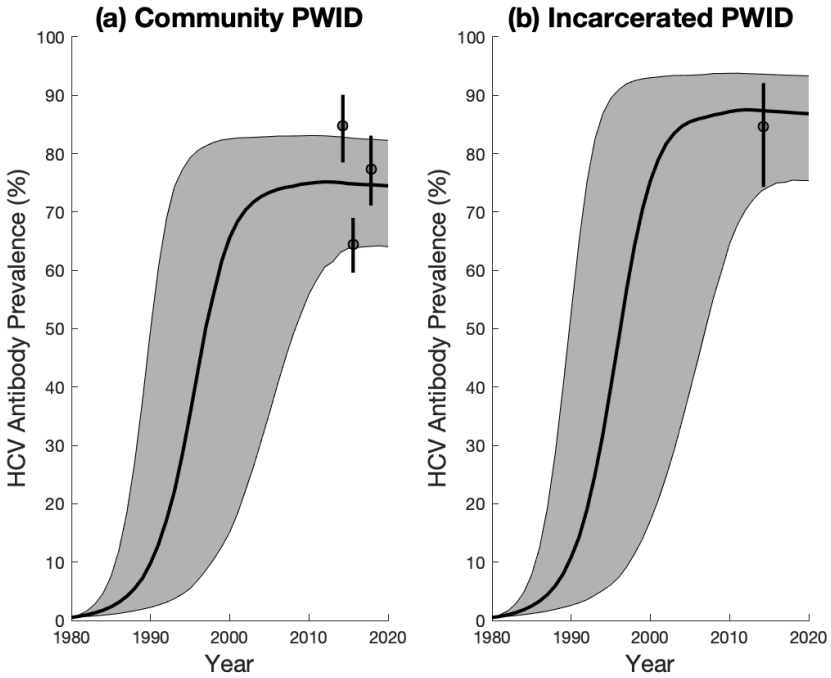


Figure M6: A comparison of model fits for Kiev with mortality estimates among current PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HIV prevalence data points with 95% confidence intervals. Model projections are reweighted to match the observed person years of HIV positive and HIV negative PWID in the study providing the data estimate.

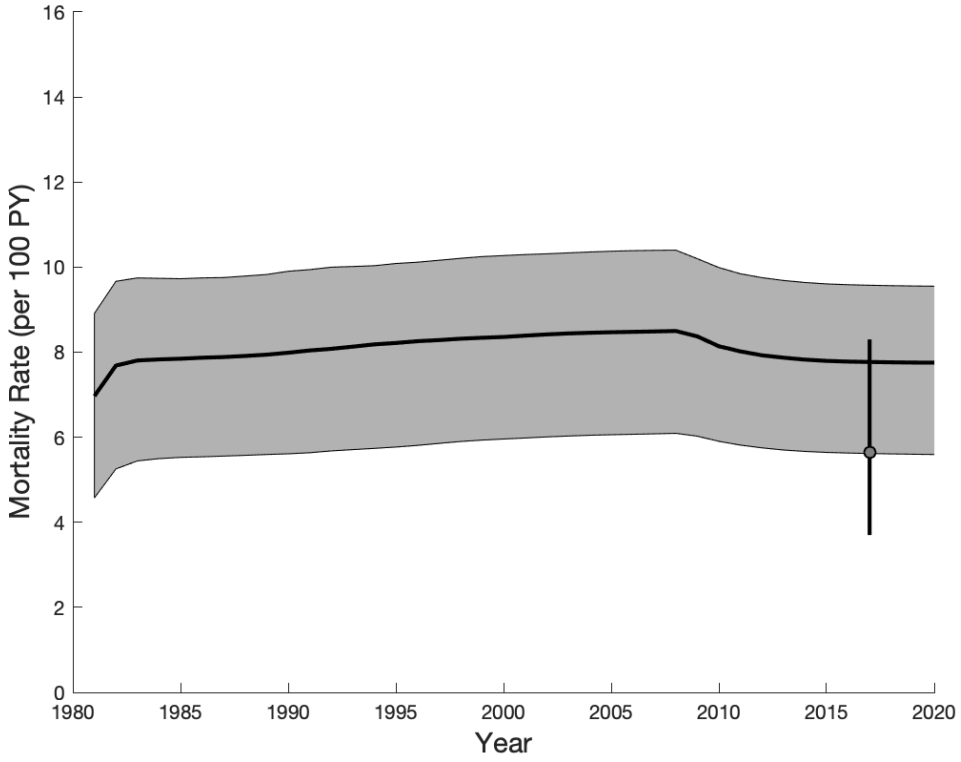


Table M6: Prior parameter distributions specific to Tehran

Parameter	Symbol	Prior	Estimates	Source
Proportion PWID who are male		Uniform (92.5-99.8)	95.8% (95%CI: 94.3-97.0) 96.5% (95%CI: 94.2-98.1) 94% 97.0% (95%CI: 93.6-98.9) 96.0% (95%CI: 94.5-97.2) 94.6%: (95%CI: 92.5-96.3) 99.3% (95%CI: 98.3-99.8)	[101] 2006/2007 [102] 2008 [103] 2003-2005 [104] 2004 [105] 2006/2007 2010 BBSS[106] 2014 BBSS[107]
Duration of injecting (years)	$\frac{1}{\nu}$	Uniform (2.0-18.2)	Mean: 4.533 Mean: 8.4 (95%CI: 7.9-8.9) Mean 8 (95%CI: 6.9-9.1) Mean: 6.4 (95%CI: 5.8-7.0) Neighbourhood 1: mean: 4.8 (95%CI: 4.0-5.6) Neighbourhood 2: mean: 4.9 (95%CI: 4.3-5.5)	[108] 2001/2002 [101] 2006/2007 [109] 2011/2012 [110] 2003/2004 [111] 2005
Age at first injection		Uniform (20-29.3)	Median: 25 Median: 26 Mean: 25.7 (95%CI: 25.2-26.2) Mean: 26.7 (95%CI: 25.7-27.7) Mean 29.3 (95%CI: 28.9-29.7) Mean: 26.1 (95%CI: 25.5-26.7) Median: 25 Median 26 (IQR: 20-30)	2010 BBSS[106] 2014 BBSS[107] [101] 2006/2007 [112] 2018 [109] 2011/2012 [110] 2003/2004 [113] 2016/2017 Maryam Alavi – unpublished data 2017/2018
% of PWID who start injecting prior to first incarceration	$\frac{\phi_{0,0}^{1,0}}{\phi_{0,0}^{4,0}}$	Uniform (43.5-98.4%)		Range of values from Kiev and Kentucky
Average length of one incarceration (year)	$\frac{12}{\tau}$	Triangular (1.0,1.14,1.5)	Mean number of incarcerations: 4.43 (95%CI: 4.13-4.75) Mean years incarcerated: 5.05 (95%CI: 4.75-5.35)	[114] 2009 - Isfahan
Annual OAT LTFU rate	κ	Normal with mean 1.71 and 95%CI: 1.54 – 1.94	Mean retention time: 7 months (95%CI: 6.2-7.8)	[115] 2007-2011
ART LTFU (per 100 py)	Γ_0	Uniform (47.5-97.3)	47.5-97.3	[116] 1997-2016; Kerman
% Of PWID on ART virally suppressed	p_s	Normal with mean 60 and 95%CI: 42.1-76.1	60% (95%CI: 42.1-76.1)	[116] 1997-2016; Kerman Assumed not to vary over time.

Table M7: Data for model calibration in Tehran

Parameter	Estimates	Source/Notes
HIV Prevalence		
HIV Prevalence among community PWID	11.4% (95%CI: 6.4-18.4)	[117] 2008
	19.4% (95%CI: 14.7-24.7)	[102] 2008
	25.7% (95%CI: 17.9-34.7)	[103] 2003-2005
	24.4% (95%CI: 20.5-28.6)	[118] 2006
	7.9% (95%CI: 3.2-15.5)	[108] 2001/2002
	15.2% (95%CI: 10.1-21.5)	[119] 2003/2004
	23.2% (95%CI: 17.6-29.5)	[120] 2004
	23.3% (95%CI: 19.9-27.1)	[121] 2006/2007
	10.7% (95%CI: 8.7-12.9)	[122] 2006/2007
	18.15% (95%CI: 15.1-21.6)	2010 BBSS[106]
	9.41% (95%CI: 7.1-12.2)	2014 BBSS[107]
Odds ratio: ever incarcerated vs never incarcerated PWID	5.57 (95%CI: 1.59-19.54)	[119] 2003/2004
	1.68 (95%CI: 0.99-2.85)	[123] 2006
	1.12 (95%CI: 0.67-1.89)	[121] 2006/2007
	6.83 (95%CI: 2.45-19.00)	2010 BBSS[106]
	8.47 (95%CI: 1.15-62.3)	2014 BBSS[107]
HIV Prevalence among incarcerated PWID	8.3% (95%CI: 6.6-10.4)	[124] 2013-2014
	17.1% (95%CI: 13.4-21.3)	[108] 2001-2002
HCV antibody prevalence		
HCV Prevalence among community PWID	50.8% (95%CI: 41.6-60.1)	[117] 2008
	36.4% (95%CI: 28.2-45.2)	[108] 2001/2002
	65.1% (95%CI: 59.0-70.9)	[102] 2008
	52.7% (95%CI: 43.0-62.3)	[103] 2003-2005
	28.3% (95%CI: 22.0-35.4)	[109] 2011/2012
	52.0% (95%CI: 44.9-59.0)	[104] 2004
	80.0% (95%CI: 76.2-83.6)	[125] 2006
	34.5% (95%CI: 31.4-37.7)	[105] 2006/2007
	61.7% (95%CI: 53.8-69.1)	Maryam Alavi – unpublished data 2018/2019
	78.7% (95%CI: 73.1-82.9%)	[121,126] 2006/2007
Odds ratio: ever incarcerated vs never incarcerated PWID	2.18 (95%CI: 1.33-3.57)	[118] 2006
	4.29 (95%CI: 2.94-6.27)	[105] 2006/2007
	2.18 (95%CI: 1.14-4.16)	Maryam Alavi – unpublished data 2018/2019
	1.35 (95%CI: 0.73-2.46)	[127] 2006/2007
HCV Prevalence among incarcerated PWID	80.6% (95%CI 76.2-84.4)	[108] 2011/2002
	40.1% (95%CI: 40.3-50.3)	[128] 1995
Odds ratio: HIV positive vs HIV negative PWID	10.28 (95%CI: 6.02-17.55)	[122] 2006/2007
	2.53 (95%CI: 1.31-4.87)	[129] 2006
Incarceration data		
% Ever incarcerated	61.1% (95%CI: 53.1-68.7)	[130] 2013/2014
	70.9% (95%CI: 67.8-73.8)	[101] 2006/2007
	72.7% (95%CI: 67.9-77.1)	[102] 2008
	61.8% (95%CI: 53.7-69.4)	[119] 2003-2004
	75.3% (95%CI: 71.1-79.2)	[118] 2006
	83.2% (95%CI: 79.7-86.3)	[121] 2006/2007

	62.9% (95%CI: 55.1-70.2)	Maryam Alavi – unpublished data 2018/2019
	80.0% (95%CI: 76.2-83.4)	2016
	80.5% (95%CI: 77.0-83.6)	2010 BBSS[106]
	84.30% (95%CI: 81.1-87.1)	2014 BBSS[107]
% Incarcerated twice or more	61.3% (95%CI: 57.2-65.2)	2010 BBSS[106]
	65.3% (95%CI: 61.3-69.1)	2014 BBSS[107]
OAT Coverage		
Proportion of PWID currently on OAT	11% (assume between 7-15%)	UNAIDS – national programme data 2017
Proportion of incarcerated PWID currently on OAT	35-45%	Based on unpublished data from Goran prison: 45% and expert opinion for Tehran: 40%
ART Coverage		
ART coverage	11% (7-19%)	[62] 2013
Mortality		
Overall mortality rate (per 100 py) among PWID	4.1 (95%CI: 1.3-6.9)	[131] 2001-2005
	4.8 (95%CI: 0-14.3)	[132] 2007
% of all deaths among PWID that are overdose	62.5% (24.5-91.5)	[131] 2003

Figure M7: A comparison of model fits for Tehran with HIV prevalence estimates among (a) PWID in the community, and (b) incarcerated PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HIV prevalence data points with 95% confidence intervals.

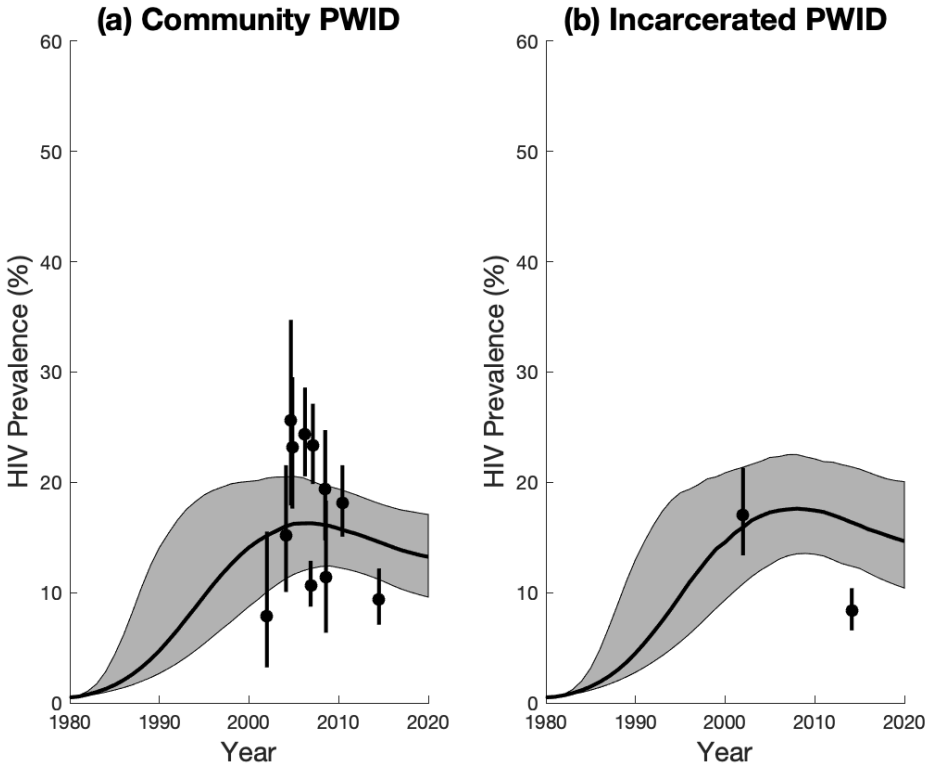


Figure M8: A comparison of model fits for Tehran with HCV prevalence estimates among (a) PWID in the community, and (b) incarcerated PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HCV prevalence data points with 95% confidence intervals.

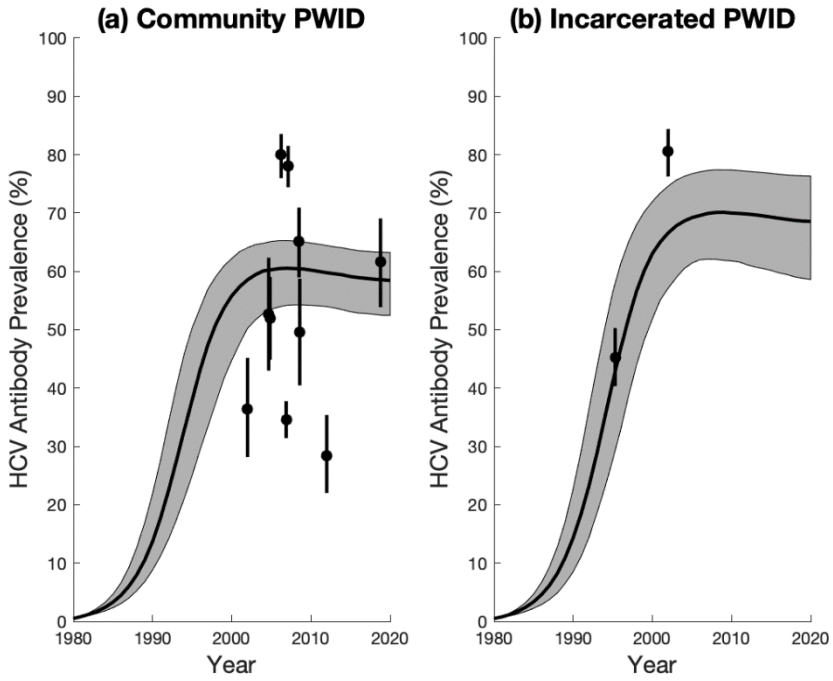
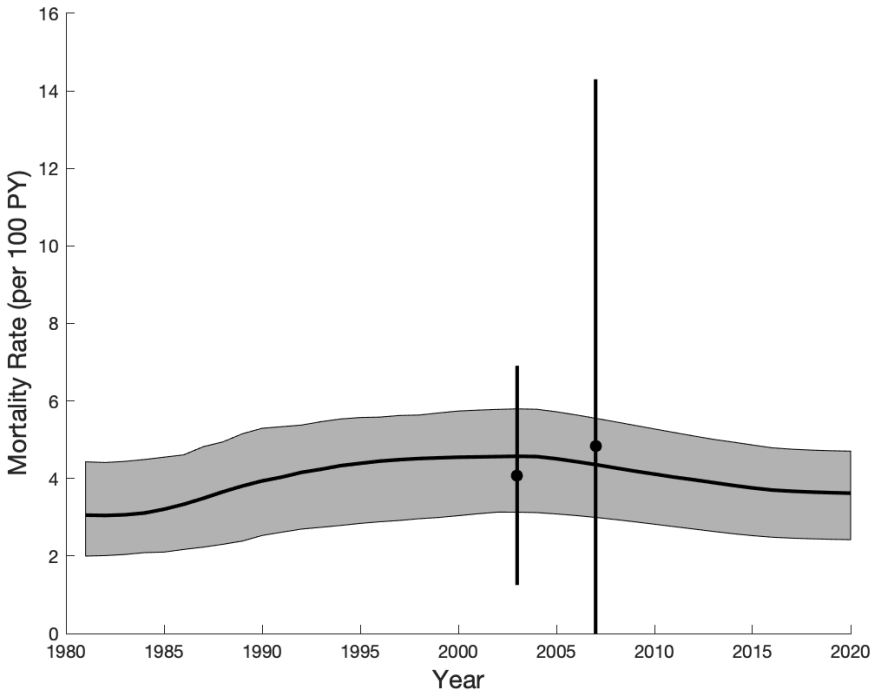


Figure M9: A comparison of model fits for Tehran with mortality estimates among current PWID. Continuous black line shows median projections from all the model fits, with the grey shaded areas showing 95% credibility intervals. Black points and whiskers show HIV prevalence data points with 95% confidence intervals.



Model Equations

$X_{i,j}^{m,n}$ and $Y_{i,j}$ are the number of PWID and ex-PWID in the model, where

- superscript m denotes incarceration status ($m = 1$, never incarcerated; $m = 2$, currently incarcerated; $m = 3$, recently released from prison (in the last 6 months); $m = 4$, previously incarcerated but not in the last 6 months)
- superscript n denotes OAT status ($n = 1$, off OAT; $n = 2$, on OAT)
- subscript i denotes HIV status ($i = 1$, Susceptible to HIV; $i = 2$, Acute HIV infection; $i = 3$, Latent HIV infection without ART; $i = 4$, Latent HIV infection and on ART; $i = 5$, AIDS without ART; $i = 6$ AIDS and on ART)
- subscript j denotes HCV status ($j = 1$, Never exposed to HCV (AB and RNA negative); $j = 2$, Previously exposed to HCV (AB positive and RNA negative); $j = 3$, Infected with F0; $j = 4$, Infected with F1; $j = 5$, Infected with F2; $j = 6$, Infected with F3; $j = 7$, Infected with F4; $j = 8$, Infected with decompensated cirrhosis ; $j = 9$, Infected with hepatocellular carcinoma)

The ordinary differential equation models can be written as

$$\frac{dX_{i,j}^{m,n}}{dt} = E_{i,j}^{m,n} + \mathrm{M}_{i,j}^{m,n} + O_{i,j}^{m,n} + I_{i,j}^{m,n} + T_{i,j}^{m,n} + D_{i,j}^{m,n} + K_{i,j}^{m,n} + H_{i,j}^{m,n}$$

$$\frac{dY_{i,j}^{m,n}}{dt} = \overline{M}_{i,j} + \overline{D}_{i,j} + \overline{H}_{i,j}$$

The terms of these differential equations represent different aspects of the model and are described below.

<u>Inflow of PWID</u>

$E_{i,j}^{m,n}$ denotes the inflow of new PWID term in the equations and is given by

$$E_{i,j}^{m,n} = \phi_{i,j}^{m,n}\theta(t)$$

Where,

- $\phi_{i,j}^{m,n}$ denotes the proportion of new PWID that enter into each group
- $\theta(t)$ denotes the number of new PWID entering the model at time t

Injecting cessation and mortality

These terms in the equations are concerned with cessation of injecting as well as overdose, suicide and other mortality. $\mathrm{M}_{i,j}^{m,n}$ and $\overline{M}_{i,j}$ denotes the terms for current PWID and ex-PWID, respectively. The terms in the equations for injecting cessation and mortality for PWID and ex-PWID are given by

$$\mathrm{M}_{i,j}^{m,1} = -(v + \mu_1 + \mu_2 + \mu_3 + \mu_4)X_{i,j}^{m,1} \qquad \text{if } m = 1,3,4;$$

$$\mathrm{M}_{i,j}^{m,2} = -(v + OAT_s^c\mu_1 + OAT_o^c\mu_2 + OAT_l^c\mu_3 + OAT_a\mu_4)X_{i,j}^{m,2} \qquad \text{if } m = 1,3,4;$$

$$\mathrm{M}_{i,j}^{2,1} = -(v + \mu_1 + R_o\mu_2 + R_i\mu_3 + R_a\mu_4)X_{i,j}^{2,1}$$

$$\mathrm{M}_{i,j}^{2,2} = -\left(v + OAT_s^p\mu_1 + OAT_o^pR_o\mu_2 + OAT_l^pR_i\mu_3 + OAT_aR_a\mu_4\right)X_{i,j}^{2,2}$$

$$\overline{M}_{i,j} = -\mu_5 Y_{i,j} + \sum_{n,m} vX_{i,j}^{m,n}$$

Where,

- v denotes the rate of cessation of injecting
- μ_1 denotes the suicide mortality rate in community PWID off OAT
- μ_2 denotes the overdose mortality rate in community PWID off OAT
- μ_3 denotes the injury mortality rate in community PWID off OAT
- μ_4 denotes the mortality rate among PWID due to other causes (not suicide/overdose/injury/HIV/HCV) in community PWID
- μ_5 denotes the mortality rate among Ex-PWID due to other causes (not suicide, overdose, injury, HIV or HCV-related death)
- OAT_s^p and OAT_s^c denote the relative risk of suicide mortality if on OAT vs off OAT whilst in prison and the community, respectively.
- OAT_o^p and OAT_o^c denote the relative risk of overdose mortality if on OAT vs off OAT whilst in prison and the community, respectively.
- OAT_l^p and OAT_l^c denote the relative risk of injury mortality if on OAT vs off OAT whilst in prison and the community, respectively.
- OAT_a denote the relative risk of other (not suicide, overdose, injury, HIV or HCV-related death) causes of mortality if on OAT vs off OAT whilst in prison and the community, respectively.

- R_o, R_i and R_a denote the relative risk of mortality due to overdose, injury and other causes, respectively, in prison compared to the community.

N.B. Overdose mortality due to overdose upon initiating or ending OAT is given in the section on "Transitions on and off OAT"; Overdose mortality in the first few weeks after release from prison is given in the section on "Transitions between incarceration states"; HCV mortality is in the section on HCV disease progression; and, HIV mortality is in the section on HIV disease progression.

Transitions on and off OAT

These terms in the equations are concerned with movement of current PWID onto and off of OAT and are denoted by $O_{i,j}^{m,n}$ which is given by:

$$O_{i,j}^{m,1} = -\epsilon^c X_{i,j}^{m,1} + \left(1 - \mu_2 (OAT_{leave} - 1)\frac{28}{365}\right)\kappa X_{i,j}^{m,2} \qquad \text{if } m = 1,3,4$$

$$O_{i,j}^{m,2} = -\kappa X_{i,j}^{m,2} + \left(1 - \mu_2 OAT_o^c (OAT_{start} - 1)\frac{28}{365}\right)\epsilon^c X_{i,j}^{m,1} \qquad \text{if } m = 1,3,4$$

$$O_{i,j}^{2,1} = -\epsilon^p X_{i,j}^{2,1} + \left(1 - R_o \mu_2 (OAT_{leave} - 1)\frac{28}{365}\right)\kappa X_{i,j}^{2,2}$$

$$O_{i,j}^{2,2} = -\kappa X_{i,j}^{2,2} + \left(1 - R_o \mu_2 OAT_o^p (OAT_{start} - 1)\frac{28}{365}\right)\epsilon^p X_{i,j}^{2,1}$$

Where,

- ϵ^c and ϵ^p denote the OAT recruitment rate for PWID in the community and prison, respectively.
- κ denotes the OAT loss to follow-up rate for PWID
- OAT_{start} denotes the relative increase in overdose mortality in the first four weeks after starting OAT
- OAT_{leave} denotes the relative increase in overdose mortality in the first four weeks after leaving OAT

Transitions between incarceration states

These terms in the equations are concerned with movement between incarceration states and are denoted by $I_{i,j}^{m,n}$ which is given by:

$$I_{i,j}^{1,1} = -\gamma_1 X_{i,j}^{1,1}$$

$$I_{i,j}^{1,2} = -OAT_{inc}\gamma_1 X_{i,j}^{1,2}$$

$$I_{i,j}^{2,1} = \gamma_1 X_{i,j}^{1,1} + \gamma_2\left(X_{i,j}^{3,1} + X_{i,j}^{4,1}\right) + (1 - p_{inc})OAT_{inc}\left(\gamma_1 X_{i,j}^{1,2} + \gamma_2\left(X_{i,j}^{3,2} + X_{i,j}^{4,2}\right)\right) - \tau X_{i,j}^{2,1}$$

$$I_{i,j}^{2,2} = p_{inc}OAT_{inc}\left(\gamma_1 X_{i,j}^{1,2} + \gamma_2\left(X_{i,j}^{3,2} + X_{i,j}^{4,2}\right)\right) - \tau X_{i,j}^{2,2}$$

$$I_{i,j}^{3,1} = \left(1 - (R_r - 1)\mu_2\frac{28}{365}\right)\tau X_{i,j}^{2,1} + (1 - p_{rel})\left(1 - OAT_o^{rel}(R_r - 1)\mu_2\frac{28}{365}\right)\tau X_{i,j}^{2,2} - (F + \gamma_2)X_{i,j}^{3,1}$$

$$I_{i,j}^{3,2} = p_{rel}\left(1 - OAT_o^{rel}OAT_o^{C}(R_r - 1)\mu_2\tfrac{28}{365}\right)\tau X_{i,j}^{2,2} - (F + \gamma_2 OAT_{inc})X_{i,j}^{3,2}$$

$$I_{i,j}^{4,1} = 2X_{i,j}^{3,1} - \gamma_2 X_{i,j}^{4,1}$$

$$I_{i,j}^{4,2} = 2X_{i,j}^{3,2} - OAT_{inc}\gamma_2 X_{i,j}^{4,2}$$

Where,

- γ_1 denotes the incarceration rate
- γ_2 denotes the re-incarceration rate
- p_{inc} denotes the proportion of PWID that are retained on OAT upon (re-)incarceration
- p_{rel} denotes the proportion of PWID that are retained on OAT upon release from prison
- R_r denotes the relative increase in overdose mortality in the first 4 weeks after prison release vs rest of time in the community
- τ denotes the rate of release from prison
- OAT_o^{rel} denotes the relative reduction in overdose mortality in the first 4 weeks after release from prison if on OAT at time of release
- OAT_{inc} denotes the relative reduction in (re-)incarceration rates if on OAT vs off OAT.
- $1/F$ is the length of the high risk period following release from prison (0.5 year)

HCV transmission

These terms in the equations are concerned with HCV transmission and are denoted by $T_{i,j}^{m,n}$, which is given by

$$T_{i,1}^{m,1} = -\beta^m X_{i,1}^{m,1} \qquad \forall\, i$$

$$T_{i,1}^{m,2} = -OAT_{HCV}\beta^m X_{i,1}^{m,2} \qquad \forall\, i$$

$$T_{1,2}^{m,1} = -(1-\alpha_-)\beta^m X_{1,2}^{m,1} + \alpha_-\beta^m X_{1,1}^{m,1}$$

$$T_{i,2}^{m,1} = -(1-\alpha_+)\beta^m X_{i,2}^{m,1} + \alpha_+\beta^m X_{i,1}^{m,1} \qquad \text{if } i \geq 2$$

$$T_{1,2}^{m,2} = -(1-\alpha_-)OAT_{HCV}\beta^m X_{1,2}^{m,2} + \alpha_- OAT_{HCV}\beta^m X_{1,1}^{m,2}$$

$$T_{i,2}^{m,2} = -(1-\alpha_+)OAT_{HCV}\beta^m X_{i,2}^{m,2} + \alpha_+ OAT_{HCV}\beta^m X_{i,1}^{m,2} \qquad \text{if } i \geq 2$$

$$T_{1,3}^{m,1} = (1-\alpha_-)\beta^m (X_{1,2}^{m,1} + X_{1,1}^{m,1})$$

$$T_{i,3}^{m,1} = (1-\alpha_+)\beta^m (X_{i,2}^{m,1} + X_{i,1}^{m,1}) \qquad \text{if } i \geq 2$$

$$T_{1,3}^{m,2} = (1-\alpha_-)OAT_{HCV}\beta^m (X_{1,2}^{m,2} + X_{1,1}^{m,2})$$

$$T_{i,3}^{m,2} = (1-\alpha_+)OAT_{HCV}\beta^m (X_{i,2}^{m,2} + X_{i,1}^{m,2}) \qquad \text{if } i \geq 2$$

$$T_{i,j}^{m,n} = 0 \qquad \text{if } j > 3$$

Where,

- β^m is the HCV force of infection for PWID in incarceration state m (see section below)
- OAT_{HCV} is the relative reduction in HCV transmission risk if on OAT compared to off OAT
- α_- is the proportion of HCV infections that spontaneously clear if HIV negative
- α_+ is the proportion of HCV infections that spontaneously clear if HIV positive

N.B. The model does not include a compartment for HCV acutely infected PWID because previous modelling indicates it contributes little to transmission, probably due to the small proportion of PWID that clear infection and the relatively short duration of the acute phase[133]. No immunity is assumed

following spontaneous clearance because the evidence is uncertain[134] and previous analyses suggested that incorporation of partial immunity has negligible impact[133,135].

HCV force of infection

The HCV force of infection for PWID in each incarceration state is denoted by β^m and is given by

$$\beta^1 = \lambda \frac{C_-^c + C_+^c}{T^c}$$

$$\beta^2 = \eta_1 \lambda \frac{C_-^p + C_+^p}{T^p}$$

$$\beta^3 = \eta_1 \lambda \frac{C_-^c + C_+^c}{T^c}$$

$$\beta^4 = \lambda \frac{C_-^c + C_+^c}{T^c}$$

Where,

$$C_-^c = \sum_{j \geq 3} \left(X_{1,j}^{1,1} + \eta_1 X_{1,j}^{3,1} + X_{1,j}^{4,1} + OAT_{HCV} \left(X_{1,j}^{1,2} + \eta_1 X_{1,j}^{3,2} + X_{1,j}^{4,2} \right) \right)$$

$$C_+^c = \eta_2 \sum_{j \geq 3} \sum_{i > 1} [X_{i,j}^{1,1} + \eta_1 X_{i,j}^{3,1} + X_{i,j}^{4,1} + OAT_{HCV} \left(X_{i,j}^{1,2} + \eta_1 X_{i,j}^{3,2} + X_{i,j}^{4,2} \right)]$$

$$T^c = \sum_{i,j} [X_{i,j}^{1,1} + \eta_1 X_{i,j}^{3,1} + X_{i,j}^{4,1} + OAT_{HCV} \left(X_{i,j}^{1,2} + \eta_1 X_{i,j}^{3,2} + X_{i,j}^{4,2} \right)]$$

$$C_-^p = \sum_{j \geq 3} (X_{1,j}^{2,1} + OAT_{HCV} X_{1,j}^{2,2})$$

$$C_+^p = \eta_2 \sum_{j \geq 3} \sum_{i > 1} (X_{i,j}^{2,1} + OAT_{HCV} X_{i,j}^{2,2})$$

$$T^p = \sum_{i,j} (X_{i,j}^{2,1} + OAT_{HCV} X_{i,j}^{2,2})$$

and

- λ is the HCV transmission rate for PWID who are not on OAT and are not currently or recently incarcerated
- η_1 is the relative increase in HIV and HCV injecting risk if PWID are currently or recently incarcerated
- η_2 is the relative increase in HCV transmissibility if PWID are HIV positive compared to HIV negative

HCV disease progression

These terms in the equations are concerned with HCV disease progression and are denoted by $D_{i,j}^{m,n}$ and $\overline{D}_{i,j}$ for current PWID and ex-PWID, respectively. These are given by

$D_{i,j}^{m,n} = 0 \qquad \text{if } j = 1,2$

$D_{i,3}^{m,n} = -\sigma_{3,4}^{i} X_{i,3}^{m,n}$

$D_{i,4}^{m,n} = -\sigma_{4,5}^{i} X_{i,4}^{m,n} + \sigma_{3,4}^{i} X_{i,3}^{m,n}$

$D_{i,5}^{m,n} = -\sigma_{5,6}^{i} X_{i,5}^{m,n} + \sigma_{4,5}^{i} X_{i,4}^{m,n}$

$D_{i,6}^{m,n} = -\sigma_{6,7}^{i} X_{i,6}^{m,n} + \sigma_{5,6}^{i} X_{i,5}^{m,n}$

$D_{i,7}^{m,n} = -(\sigma_{7,8}^{i} + \sigma_{7,9}^{i}) X_{i,7}^{m,n} + \sigma_{6,7}^{i} X_{i,6}^{m,n}$

$D_{i,8}^{m,n} = -(\sigma_{8,9}^{i} + \mu_{DC}^{i}) X_{i,8}^{m,n} + \sigma_{7,8}^{i} X_{i,7}^{m,n}$

$D_{i,9}^{m,n} = -\mu_{HCC} X_{i,9}^{m,n} + \sigma_{7,9}^{i} X_{i,7}^{m,n} + \sigma_{8,9}^{i} X_{i,8}^{m,n}$

and

$\overline{D}_{i,j} = 0 \qquad \text{if } j = 1,2$

$\overline{D}_{i,3} = -\sigma_{3,4}^{i} Y_{i,3}$

$\overline{D}_{i,4} = -\sigma_{4,5}^{i} Y_{i,4} + \sigma_{3,4}^{i} Y_{i,3}$

$\overline{D}_{i,5} = -\sigma_{5,6}^{i} Y_{i,5} + \sigma_{4,5}^{i} Y_{i,4}$

$$\overline{D}_{i,6} = -\sigma^i_{6,7} Y_{i,6} + \sigma^i_{5,6} Y_{i,5}$$

$$\overline{D}_{i,7} = -(\sigma^i_{7,8} + \sigma^i_{7,9}) Y_{i,7} + \sigma^i_{6,7} Y_{i,6}$$

$$\overline{D}_{i,8} = -(\sigma^i_{8,9} + \mu^i_{DC}) Y_{i,8} + \sigma^i_{7,8} Y_{i,7}$$

$$\overline{D}_{i,9} = -\mu_{HCC} Y_{i,9} + \sigma^i_{7,9} Y_{i,7} + \sigma^i_{8,9} Y_{i,8}$$

Where,

- $\sigma^i_{p,q}$ denotes the rate of progressing from HCV disease state p to HCV disease state q if in HIV state i
- μ^i_{DC} denotes the mortality rate for HCV infected individuals with decompensated cirrhosis in HIV state i
- μ_{HCC} denotes the mortality rate for HCV infected individuals with hepatocellular carcinoma (HCC).

HIV transmission

These terms in the equations are concerned with HIV transmission and are denoted by $K^{m,n}_{i,j}$, which is given by

$$K^{m,1}_{1,j} = -(\Lambda^{\mathrm{m}}_{inj} + \Lambda^m_{sex}) X^{m,1}_{1,j}$$

$$K^{m,1}_{2,j} = (\Lambda^{\mathrm{m}}_{inj} + \Lambda^m_{sex}) X^{m,1}_{1,j}$$

$$K^{m,2}_{1,j} = -(\mathrm{OAT}_{\mathrm{HIV}} \Lambda^{\mathrm{m}}_{inj} + \Lambda^m_{sex}) X^{m,2}_{1,j}$$

$$K^{m,2}_{2,j} = (\mathrm{OAT}_{\mathrm{HIV}} \Lambda^{\mathrm{m}}_{inj} + \Lambda^m_{sex}) X^{m,2}_{1,j}$$

$$K^{m,n}_{i,j} = 0 \qquad \text{if } i \geq 3$$

Where,

- $\Lambda^{\mathrm{m}}_{inj}$ is the HIV injecting force of infection for PWID in incarceration state m (see section below)
- $\Lambda^{\mathrm{m}}_{sex}$ is the HIV sexual force of infection for PWID in incarceration state m (see section below)
- OAT_{HIV} is the relative reduction in HIV injecting transmission risk if on OAT compared to off OAT

HIV injecting force of infection

The HIV injecting force of infection for PWID in each incarceration state m is denoted by Λ_{inj}^{m} and is given by

$$\Lambda_{inj}^{1} = \zeta \frac{L_1^c + L_2^c + L_3^c}{N^c}$$

$$\Lambda_{inj}^{2} = \eta_1 \zeta \frac{L^p}{N^p}$$

$$\Lambda_{inj}^{3} = \eta_1 \zeta \frac{L_1^c + L_2^c + L_3^c}{N^c}$$

$$\Lambda_{inj}^{4} = \zeta \frac{L_1^c + L_2^c + L_3^c}{N^c}$$

Where,

$$L_1^c = \omega_a \sum_j [X_{2,j}^{1,1} + \eta_1 X_{2,j}^{3,1} + X_{2,j}^{4,1} + OAT_{HIV}(X_{2,j}^{1,2} + \eta_1 X_{2,j}^{3,2} + X_{2,j}^{4,2})]$$

$$L_2^c = \sum_j [X_{3,j}^{1,1} + \eta_1 X_{3,j}^{3,1} + X_{3,j}^{4,1} + OAT_{HIV}(X_{3,j}^{1,2} + \eta_1 X_{3,j}^{3,2} + X_{3,j}^{4,2})]$$

$$L_3^c = \Delta \sum_{i=4,6} \sum_j [\mathrm{A}_0(X_{i,j}^{1,1} + \eta_1 X_{i,j}^{3,1} + X_{i,j}^{4,1}) + \mathrm{A}_1 OAT_{HIV}(X_{i,j}^{1,2} + \eta_1 X_{i,j}^{3,2} + X_{i,j}^{4,2})]$$

$$N^c = \sum_{i \neq 5} \sum_j [X_{i,j}^{1,1} + \eta_1 X_{i,j}^{3,1} + X_{i,j}^{4,1} + OAT_{HIV}(X_{i,j}^{1,2} + \eta_1 X_{i,j}^{3,2} + X_{i,j}^{4,2})]$$

$$L^p = \sum_j \left(\omega_a X_{2,j}^{2,1} + X_{3,j}^{2,1} + \Delta A_0\left(X_{4,j}^{2,1} + X_{6,j}^{2,1}\right) + OAT_{HIV}\left(\omega_a X_{2,j}^{2,2} + X_{3,j}^{2,2} + \Delta A_1\left(X_{4,j}^{2,2} + X_{6,j}^{2,2}\right)\right)\right)$$

$$N^p = \sum_{i \neq 5} \sum_j (X_{i,j}^{2,1} + OAT_{HIV} X_{i,j}^{2,2})$$

and,

- ζ denotes the HIV transmission rate for injecting for PWID who are not on OAT and are not currently or recently incarcerated

- ω_a denotes the relative increase in HIV transmissibility if in the acute stage of infection compared to the latent stage of infection
- A_0 denotes the relative reduction in HIV transmission for sexual transmission if on ART whilst not on OAT (see section below on Effectiveness of ART)
- A_1 denotes the relative reduction in HIV transmission for sexual transmission if on ART whilst on OAT (see section below on Effectiveness of ART)
- Δ denotes the relative reduction in the effectiveness of ART for reducing HIV transmission through injecting compared to sexual transmission.

HIV sexual force of infection

The HIV sexual force of infection for PWID in each incarceration state is denoted by Λ_{sex}^{m} and is given by

$$\Lambda_{sex}^{m} = \pi \frac{\sum_{m\neq 2}\sum_{j}\left(\omega_a(X_{2,j}^{m,1}+X_{2,j}^{m,2})+X_{3,j}^{m,1}+X_{3,j}^{m,2}+A_0\left(X_{4,j}^{m,1}+X_{6,j}^{m,1}\right)+A_1\left(X_{4,j}^{m,2}+X_{6,j}^{m,2}\right)\right)}{\sum_{m\neq 2}\sum_{n}\sum_{j}\sum_{i\neq 5}X_{i,j}^{m,n}} \quad \text{if } m = 1,3,4$$

$$\Lambda_{sex}^{m} = 0 \quad \text{if } m = 2$$

Where π denotes the sexual HIV transmission rate.

Effectiveness of ART for reducing HIV sexual transmission

If p_s denotes the proportion of PWID on ART but not OAT who are virally supressed, and r_s denotes the odds ratio of viral suppression when on OAT compared to PWID not on OAT then the proportion of PWID on ART with viral suppression when on OAT is given by

$$p_s^* = p_s r_s/(1 + p_s(r_s - 1)).$$

To determine the decrease in HIV transmission risk among virally suppressed and unsuppressed PWID on ART, we estimated the log difference between the baseline plasma viral load ($PVL - v_b$) for PWID off ART, and PWID on ART with suppressed (v_s) PVL $\Delta_s = v_b - v_s$, or unsuppressed (v_u) PVL $\Delta_u = v_b - v_u$. Because prior studies[93,136] suggest HIV transmission risk increases (factor r_t) for each log increase in PVL, these log differences in PVL were used to estimate the relative decrease in transmission risk among virally suppressed (e_s) and unsuppressed (e_u) PWID on ART:

$e_s = 1/(r_t^{\Delta_s})$
$e_u = 1/(r_t^{\Delta_u})$

The average reduction in HIV transmission by ART for PWID off OAT (A_0) or on OAT (A_1) is then given by

$A_0 = p_s e_s + (1 - p_s)e_u$

$A_1 = p_s^* e_s + (1 - p_s^*)e_u$

Where,

- p_s^* and p_s denote the proportion of PWID on ART who are virally supressed if on and off OAT, respectively
- e_s and e_u denote the relative decrease in transmission risk among virally suppressed and unsuppressed PWID on ART, respectively, compared to those not on ART. e_s can take values between 0.01 and 0.21 (i.e. between a 79% and 99% reduction) and e_u can take values between 0.07 and 1.0 (i.e. between 0% and 93% reduction).

HIV disease progression

These terms in the equations are concerned with HIV disease progression and are denoted by $H_{i,j}^{m,n}$ and $\overline{H}_{i,j}$ for current PWID and ex-PWID, respectively. These are given by

$H_{1,j}^{m,n} = 0$

$H_{2,j}^{m,n} = -\delta_a X_{2,j}^{m,n}$

$H_{3,j}^{m,n} = -(\delta_l + \Omega_\mathrm{n})X_{3,j}^{m,n} + \delta_a X_{2,j}^{m,n} + \Gamma_\mathrm{n} X_{4,j}^{m,n}$

$H_{4,j}^{m,n} = -(Z_n \delta_l + \Gamma_\mathrm{n})X_{4,j}^{m,n} + \Omega_\mathrm{n} X_{3,j}^{m,n}$

$H_{5,j}^{m,n} = -(\mu_{HIV} + \Omega_\mathrm{n})X_{5,j}^{m,n} + \delta_l X_{3,j}^{m,n} + \Gamma_\mathrm{n} X_{6,j}^{m,n}$

$H_{6,j}^{m,n} = -(Z_n \mu_{HIV} + \Gamma_\mathrm{n})X_{6,j}^{m,1} + \Omega_\mathrm{n} X_{5,j}^{m,n} + Z_n \delta_l X_{4,j}^{m,n}$

and,

$$\overline{H}_{1,j} = 0$$

$$\overline{H}_{2,j} = -\delta_a Y_{2,j}$$

$$\overline{H}_{3,j} = -(\delta_l + \Omega_2)Y_{3,j} + \delta_a Y_{2,j} + \Gamma_2 Y_{4,j}$$

$$\overline{H}_{4,j} = -(Z_2\delta_l + \Gamma_2)Y_{4,j} + \Omega_2 Y_{3,j}$$

$$\overline{H}_{5,j} = -(\mu_{HIV} + \Omega_2)Y_{5,j} + \delta_l Y_{3,j} + \Gamma_2 Y_{6,j}$$

$$\overline{H}_{6,j} = -(Z_2\mu_{HIV} + \Gamma_2)Y_{6,j} + \Omega_2 Y_{5,j} + Z_2\delta_l Y_{4,j}$$

where,

- δ_a is the rate of progressing from acute HIV infection to latent HIV infection.
- δ_l is the rate of progressing from latent HIV infection to AIDS if not on ART
- μ_{HIV} is the mortality rate from AIDS if not on ART
- Ω_n is the rate of enrolling onto ART if in OAT group n
- Γ_n is the loss to follow-up rate from ART if in OAT group n
- Z_n is the relative reduction in HIV progression and mortality if on ART and in OAT group n

Effectiveness of ART for reducing HIV progression

Z_1 and Z_2 denote the relative reduction in HIV progression and mortality if on ART for those off or on OAT, respectively and are given by:

$$Z_1 = (p_s + (1 - p_s)t_s)t_p$$

$$Z_2 = (p_s^* + (1 - p_s^*)t_s)t_p$$

Where,

- p_s^* and p_s denote the proportion of PWID on ART who are virally supressed if on and off OAT, respectively (see section on 'Effectiveness of ART for reducing HIV sexual transmission')
- t_p denotes the reduction in HIV progression if on ART and virally supressed compare to those not on ART

- t_s denotes the relative increase in HIV progression if on ART and not virally supressed compared to those on ART who are virally supressed.

Model Outcomes

The number of deaths due to each cause is calculated by integrating between 2020 and 2040 the terms in the model equations related to mortality due to that cause. For example, the number of HCV deaths over 2020 and 2040 is calculated as

$$\int_{2020}^{2040} \sum_m \sum_n \sum_i (\mu_{DC}^i X_{i,8}^{m,n} + \mu_{HCC} X_{i,9}^{m,n}) + \sum_i (\mu_{DC}^i Y_{i,8} + \mu_{HCC} Y_{i,9})\, dt,$$

The number of total deaths that occur between 2020 and 2040 is then given by summing the number of deaths that occur over 2020-2040 due to each cause.

The percentage of deaths averted by a scenario with OAT compared to a scenario without OAT is given by:

$$\frac{D_{No\ OAT} - D_{OAT}}{D_{No\ OAT}} * 100$$

Where,
$D_{No\ OAT}$ is the number of deaths that occur in a scenario where there is no OAT from 2020 onwards.
D_{OAT} is the number of deaths that occur in a scenario with OAT.

Finally, Life-years gained per 1000 PWID by a scenario with OAT compared to a scenario without OAT is given by:

$$\frac{L_{OAT} - L_{No\ OAT}}{N_{2020}} * 1000$$

Where,
N_{2020} is the number of PWID in the model at the start of 2020.
L_{OAT} the total number of life years in the model between 2020 and 2040 for a scenario with OAT
$L_{No\ OAT}$ the total number of life years in the model between 2020 and 2040 for a scenario where there is no OAT from 2020 onwards.

The number of life-years in the model between 2020 and 2040 is calculated by integrating the modelled population size between 2020 and 2040, i.e.

$$\int_{2020}^{2040} \sum_m \sum_n \sum_i \sum_j X_{i,j}^{m,n} + \sum_i \sum_j Y_{i,j}\, dt$$

It is important to note that making model projections over 20 years involves assuming that incarceration dynamics and risk behaviours associated with injecting drug use remain the same and that interventions that could impact mortality (such as naloxone) or disease transmission (such as ART) are not introduced or scaled-up. Additional model projections suggest that the impact of scaling-up OAT on mortality reduces by at most 20% (in Kiev) if we consider a shorter time frame of 10 years. The primary reason why the impact is lowered over 10 years is that the impact of scaling-up OAT on HIV deaths is significantly

reduced (by an average of 50% in Kiev) due to there being less time to accrue reductions in HIV deaths as a consequence of reductions in HIV transmission (which was the most important effect for reducing mortality in Kiev).

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